

Janssen Research & Development***Clinical Protocol**

A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Intranasal Esketamine Plus an Oral Antidepressant in Elderly Subjects with Treatment-resistant Depression

Trial of Rapid-acting Intranasal Esketamine for Treatment-resistant Maajor Depressive Disorder
(TRANSFORM-3)

**Protocol ESKETINTRD3005; Phase 3
AMENDMENT 3****JNJ-54135419 (esketamine)**

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This compound is being investigated in Phase 3 clinical studies.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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TABLE OF CONTENTS

TABLE OF CONTENTS	2
LIST OF ATTACHMENTS	4
LIST OF IN-TEXT TABLES AND FIGURES	5
PROTOCOL AMENDMENTS	6
SYNOPSIS	32
TIME AND EVENTS SCHEDULE (Screening/Prospective Observational Phase and Double-blind Induction Phase).....	44
TIME AND EVENTS SCHEDULE (Follow-up Phase)	49
ABBREVIATIONS	51
1. INTRODUCTION.....	53
1.1. Background	54
1.1.1. Summary of Nonclinical Findings	54
1.1.2. Clinical Studies	57
1.1.2.1. Pharmacokinetics and Product Metabolism	57
1.1.2.2. Pharmacodynamics and Efficacy	59
1.1.2.3. Safety and Tolerability	61
1.1.3. Marketing Experience	66
1.2. Active Comparators in Double-blind Induction Phase	66
1.2.1. Selective Serotonin Reuptake Inhibitors.....	67
1.2.1.1. Escitalopram	67
1.2.1.2. Sertraline	67
1.2.2. Serotonin and Norepinephrine Reuptake Inhibitors	68
1.2.2.1. Duloxetine.....	68
1.2.2.2. Venlafaxine Extended-release.....	69
1.3. Overall Rationale for the Study	70
2. OBJECTIVES AND HYPOTHESIS	70
2.1. Objectives	70
2.2. Hypothesis	71
3. STUDY DESIGN AND RATIONALE	71
3.1. Overview of Study Design.....	71
3.2. Study Design Rationale.....	74
3.2.1. Study Population.....	74
3.2.2. Study Phases.....	75
3.2.3. Blinding and Randomization.....	77
3.2.4. Treatment Groups and Dose Selection	77
3.2.5. Efficacy Measures	79
3.2.6. Safety Evaluations	79
3.2.7. Other Assessments	81
3.2.8. Pharmacokinetic Assessments.....	81
3.2.9. Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations	81
4. STUDY POPULATION	82
4.1. Inclusion Criteria	82
4.2. Exclusion Criteria	84
4.3. Prohibitions and Restrictions	90
5. TREATMENT ALLOCATION AND BLINDING.....	91

6. DOSAGE AND ADMINISTRATION	92
6.1. Screening/Prospective Observational Phase	92
6.2. Double-Blind Induction Phase.....	93
6.2.1. Guidance for Blood Pressure Monitoring on Intranasal Treatment Session Days	95
6.3. Follow-up Phase	96
7. TREATMENT COMPLIANCE.....	96
8. PRESTUDY AND CONCOMITANT THERAPY	97
9. STUDY EVALUATIONS	98
9.1. Study Procedures.....	98
9.1.1. Overview	98
9.1.2. Screening/Prospective Observational Phase	99
9.1.3. Double-Blind Induction Phase	101
9.1.4. Follow-up Phase	102
9.2. Efficacy.....	103
9.2.1. Evaluations	103
9.2.1.1. Primary Efficacy Evaluation.....	103
9.2.1.2. Secondary Efficacy Evaluations (Clinician-completed)	103
9.2.1.2.1. CGI-S	103
9.2.1.3. Other Secondary Efficacy Evaluations (Patient-reported Outcomes)	104
9.2.1.3.1. EQ-5D-5L	104
9.2.2. Endpoints.....	104
9.2.2.1. Primary Endpoint.....	104
9.2.2.2. Secondary Endpoints	104
9.3. Pharmacokinetics.....	104
9.3.1. Evaluations	105
9.3.2. Analytical Procedures	105
9.3.3. Pharmacokinetic Parameters	105
9.4. Pharmacokinetic/Pharmacodynamic Evaluations.....	105
9.5. Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations.....	105
9.6. Safety Evaluations	106
9.7. Other Evaluations.....	114
9.8. Sample Collection and Handling.....	115
10. SUBJECT COMPLETION/WITHDRAWAL	116
10.1. Completion	116
10.2. Withdrawal From the Study.....	116
10.3. Withdrawal From the Use of Samples in Future Research.....	117
11. STATISTICAL METHODS.....	117
11.1. Subject Information	117
11.2. Sample Size Determination	118
11.3. Interim Analysis for Sample Size Re-estimation or Stopping for Futility.....	118
11.4. Efficacy Analyses	119
11.5. Pharmacokinetic Analyses.....	119
11.6. Pharmacokinetic/Pharmacodynamic Analyses.....	120
11.7. Biomarker and Pharmacogenomic Analyses	120
11.8. Safety Analyses	120
11.9. Independent Data Monitoring Committee	122
12. ADVERSE EVENT REPORTING	122
12.1. Definitions	123
12.1.1. Adverse Event Definitions and Classifications	123
12.1.2. Attribution Definitions.....	124
12.1.3. Severity Criteria	124
12.2. Special Reporting Situations.....	125
12.3. Procedures.....	125

12.3.1.	All Adverse Events.....	125
12.3.2.	Serious Adverse Events	126
12.3.3.	Pregnancy.....	127
12.4.	Contacting Sponsor Regarding Safety.....	127
13.	PRODUCT QUALITY COMPLAINT HANDLING.....	127
13.1.	Procedures.....	128
13.2.	Contacting Sponsor Regarding Product Quality	128
14.	STUDY DRUG INFORMATION.....	128
14.1.	Physical Description of Study Drug(s)	128
14.2.	Packaging	129
14.3.	Labeling.....	130
14.4.	Preparation, Handling, and Storage.....	130
14.5.	Drug Accountability	130
15.	STUDY-SPECIFIC MATERIALS.....	131
16.	ETHICAL ASPECTS	131
16.1.	Study-specific Design Considerations	131
16.2.	Regulatory Ethics Compliance.....	134
16.2.1.	Investigator Responsibilities	134
16.2.2.	Independent Ethics Committee or Institutional Review Board (IEC/IRB).....	134
16.2.3.	Informed Consent	135
16.2.4.	Privacy of Personal Data	136
16.2.5.	Long-Term Retention of Samples for Additional Future Research	137
16.2.6.	Country Selection	137
17.	ADMINISTRATIVE REQUIREMENTS	137
17.1.	Protocol Amendments.....	137
17.2.	Regulatory Documentation	138
17.2.1.	Regulatory Approval/Notification	138
17.2.2.	Required Prestudy Documentation.....	138
17.3.	Subject Identification, Enrollment, and Screening Logs	139
17.4.	Source Documentation.....	139
17.5.	Case Report Form Completion	140
17.6.	Data Quality Assurance/Quality Control	140
17.7.	Record Retention	141
17.8.	Monitoring	141
17.9.	Study Completion/Termination.....	142
17.9.1.	Study Completion	142
17.9.2.	Study Termination.....	142
17.10.	On-site Audits.....	142
17.11.	Use of Information and Publication	143
REFERENCES.....		145
INVESTIGATOR AGREEMENT		157

LIST OF ATTACHMENTS

Attachment 1:	Prohibited Concomitant Medications with Intranasal Study Medication (Esketamine or Placebo).....	150
Attachment 2:	New York Heart Association Classification of Cardiac Disease.....	153
Attachment 3:	Oral Antidepressant Titration Schedule for Double-Blind Induction Phase.....	154
Attachment 4:	Anticipated Events.....	155

LIST OF IN-TEXT TABLES AND FIGURES**TABLES**

Table 1:	Adverse Reactions Listed as Very Common, Common, or Frequent Occurrences in the Product Information of Anesthetic Ketamine and Esketamine	62
Table 2:	Mean Supine Blood Pressure and Heart Rate - Cohort 1 (ESKETINTRD1012).....	63
Table 3:	Intranasal Treatment Sessions Administration During the Double-blind Induction Phase	93
Table 4:	Dose Titration of Intranasal Esketamine*	94
Table 5:	Volume of Blood to Be Collected From Each Subject	99

FIGURES

Figure 1:	Study Design for ESKETINTRD3005	74
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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	10 March 2015
Amendment 1	08 June 2015
Amendment 2	10 January 2016
Amendment 3	18 July 2016

Amendments below are listed beginning with the most recent amendment.

Amendment 3 (18 July 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to improve recruitment while maintaining the integrity of the study. Changes are made that relate to the elderly population specifically (which differ in some aspects from younger patients) not included in the original protocol.

Applicable Section(s)	Description of Change(s)
Rationale: Montgomery-Asberg Depression Rating Scale (MADRS) scores in the elderly, per multiple expert opinions are lower than in younger patients. This difference is attributed to the tendency of the elderly to minimize symptoms. Therefore, a lower MADRS total cut-off score of 24 will be used for the elderly to align with a MADRS total score of 28 used in younger subjects.	
Synopsis Overview of Study Design; Synopsis Study Population; 3.1. Overview of Study Design; 3.2.1. Study Population; 4.1. Inclusion Criterion; 6.1. Screening/Prospective Observational Phase; 9.1.2. Screening/Prospective Observational Phase	MADRS total score changed from ≥ 28 to ≥ 24 , wherever the original value of 28 occurs.
Rationale: The Inventory of Depressive Symptomatology-Clinician rated, 30-item scale (IDS-C30) scores in the elderly, as per multiple expert opinions, are lower than in younger subjects, because of the tendency to minimize symptoms (as with the MADRS scores). Therefore, a lower IDS-C30 cut-off score of 31 for the elderly will be more aligned with the MADRS total score of ≥ 24 that will be used in the elderly.	
Synopsis Study Population; 3.2.1. Study Population; 4.1. Inclusion Criterion; 9.1.2. Screening/Prospective Observational Phase	IDS-C30 score changed from ≥ 34 to ≥ 31 , wherever the original value of 34 occurs.

Applicable Section(s)	Description of Change(s)
	<p>Rationale: Criteria for the minimum number of oral antidepressant treatments in the current episode of depression with non-response at the start of the Screening/Prospective Observational Phase, has been revised from ≥ 2 to ≥ 1. The elderly are more likely to have longer episodes of depression, and to have been on more oral antidepressants during the episode, than younger subjects. Therefore, the criteria for the maximum number of oral antidepressant treatments in the current episode of depression with non-response at the start of the Screening/Prospective Observational Phase, has been revised from ≤ 5 to ≤ 8. This change is supported by discussions with multiple experts in geriatric psychiatry.</p>
Synopsis Study Population; 3.2.1. Study Population; 4.1. Inclusion Criterion; 9.1.2. Screening/Prospective Observational Phase	Change in the number of oral antidepressants allowed during the current episode from ≥ 2 to ≤ 5 to ≥ 1 to ≤ 8 .
	<p>Rationale: Patients with Parkinson's disease were previously excluded as some have cognitive impairment. However, many patients with Parkinson's disease who suffer from depression do not have cognitive impairment, and the exclusion criteria has therefore, been revised to allow these patients to be included in the study.</p>
Synopsis Study Population; 4.2. Exclusion Criteria	<p>Exclusion Criterion no. 12 has been modified: The text previously stated that subjects with Parkinson's will be excluded.</p> <p>The text has been revised (new text in bold): 'Subjects with Parkinson's disease with clinical evidence of cognitive impairment will be excluded'.</p>
	<p>Rationale: Medical stabilization, allowed during the Screening/Prospective Observation period, may take longer in the elderly where changes are slower.</p>
Synopsis Overview of Study Design; Time & Events Table footnote (a);	The text has been revised to indicate that the 3 week period during the screening/prospective observational phase may be used for optimization of medical management if needed to facilitate subject participation:
3.1. Overview of Study Design; 3.2.2. Study Phases; 9.1.2 Screening/Prospective Observational Phase	<p>If clinically indicated, a subject's current antidepressant treatment(s) may be tapered and discontinued over an additional, optional period of up to 3 weeks, per the local prescribing information or per clinical judgment.</p> <p>The following text has been added: "This 3-week period may also be used to optimize medical management if needed to facilitate subject participation (eg, treatment of blood pressure or diabetes, wean from other medications, etc.). In such cases, if there is no planned taper, the oral regimen should be continued in the interim and then discontinued by Day 1 of the double-blind induction phase. "</p>
	<p>Rationale: Testing is significantly slower in the elderly population and subjects frequently complain of fatigue. Cognition testing, in particular, takes longer in the elderly than in the younger subject population. It is considered that a baseline may still be established, if values for cognition testing are obtained just prior to the initial date for the Double-Blind Induction Phase (Visit 2.1), rather than on the actual date itself.</p>
Time & Events Schedule, Screening/Prospective Observational Phase	Changes to the text added to allow for some of the assessments (eg, cognition) to take place either during the last visit in the Screening/Prospective Observational Phase (Visit 1.3) or prior to the initial visit for the Double-Bind Phase (Visit 2.1).
Legend s)	Addition of a footnote (s) by cognition testing to indicate that these tests can precede Visit 2.1.

Applicable Section(s)	Description of Change(s)
Rationale: Following discussions with a leading expert within the disease area, a decision has made to remove the Smell Threshold test, as this is operationally burdensome to perform and not required for the elderly population.	
Synopsis Safety Evaluations; Synopsis Statistical Methods; Time & Events Schedule; 3.2.6. Safety Evaluations; 9.6. Safety Evaluations; 11.8. Safety Analyses	Removal of Smell Threshold test throughout the study
Rationale: To decrease the patient burden, the UPSIT will be assessed prior to and post treatment, only.	
Time & Events Schedule	The UPSIT will be assessed on Visit 1.2. of the Screening/Prospective/Observational Phase (prior to treatment), and on either Visit 2.9 at the end of the Double-Blind Treatment Phase or at the Early Withdrawal (EW) visit <u>Change:</u> The UPSIT will not be assessed on Visit 2.5. Double-Blind Induction Phase.
Rationale: Following discussions with a leading expert within the disease area, it was decided that 3 booklets instead of the original 4 booklets were sufficient to generate UPSIT data for the elderly population, while removal of one of the booklets will reduce the operational burden for the elderly subjects.	
9.6. Safety Evaluations	The description of the UPSIT test has been changed to consist of 3 booklets instead of the original 4 booklets.
Rationale: Following discussions with a leading expert within the disease area, it was decided that data from the UPSIT was only required from 25% of subjects in the study, and that this would be sufficient to assess any potential change in smell in this population. This was based on the expectation that at least 50% of elderly subjects will have some diminution of smell (not actual anosmia). Therefore, even if half of the subjects have anosmia (fewer expected) at least 25% of the subjects will be able to be evaluated.	
4.2. Exclusion Criteria	Exclusion criterion no. 7 has been deleted. An UPSIT score is not exclusionary
Rationale: Analysis of data from elderly subjects in the Phase 3 clinical trial ESKETIN3004, and the Phase 1 clinical trials ESKETINTRD1003 and ESKETINTRD1012, did not show an effect of esketamine on the PR interval, as assessed by electrocardiography.	
4.2. Exclusion Criteria	Exclusion criterion no. 13.2 has been modified: The following text indicated has been deleted: ‘Evidence of 2 nd and 3 rd degree AV block, or 1 st degree AV block with PR interval >200 msec (if the initial PR interval is <240 msec, may repeat the ECG once and use average of both readings), complete left bundle branch block (LBBB) or complete right bundle branch block (RBBB).

Applicable Section(s)	Description of Change(s)
Rationale: The Patient Health Questionnaire-9 item (PHQ-9) and the Sheehan Disability Scale (SDS), will not be used to evaluate efficacy. This will reduce patient burden, without having a marked impact on the data generated from this study.	
Synopsis Efficacy Evaluations/Endpoints; Synopsis Statistical Methods; Time & Events Schedule; 3.2.5. Efficacy Measures; 9.2.1. Evaluations; 9.2.1.2. Key Secondary Efficacy Evaluations (Patient Reported) 9.2.2.2. Secondary Endpoints; 11.4. Efficacy Analyses;	Reference to the Patient Health Questionnaire-9 item (PHQ-9) scale and the Sheehan Disability Scale (SDS) was removed throughout.
Rationale: To improve recruitment, the antidepressant treatment requirements at study entry (ie, time of signing the ICF) in inclusion criterion no. 3 were changed. In addition, the definition of nonresponse at the end of the screening/prospective observational phase was revised.	
4.1. Inclusion Criteria	<p data-bbox="613 764 1338 825">Inclusion criteria no.3 has been revised as follows (bold text added, strikethrough text deleted):</p> <p data-bbox="613 844 1435 1115">At the start of the screening/prospective/observational phase, subject must have had nonresponse ($\leq 25\%$ improvement) to ≥ 1 but ≤ 8 (if current episode is > 2 years, upper limit applicable to only the last 2 years) oral antidepressant treatments in the current episode of depression, assessed using the MGH-ATRQ and confirmed by documented records (eg, medical/pharmacy/prescription records or a letter from a treating physician, etc). In addition, subject is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose.</p> <ul data-bbox="662 1119 1435 1661" style="list-style-type: none"> - For specific tricyclic antidepressants which are ongoing and being taken at a dose below the MGH-ATRQ minimum therapeutic dose, a blood level that is within the therapeutic (antidepressant) range, is acceptable to establish the adequacy of the antidepressant treatment. - Subjects must be adherent to the continued oral antidepressant treatment medication(s) through the screening/prospective observational phase, as documented on the PAQ. Missing ≥ 4 days of antidepressant medication in the prior 2 week period will be considered as inadequate adherence. - Subjects who are nonresponders to their current oral antidepressant medication(s) from the screening/prospective observational phase (as assessed by independent, remote raters) may be eligible for randomization if all other entry criteria are met. Non-response at the end of the screening/prospective observational phase is defined as $\leq 25\%$ improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥ 24 on Week 2 and Week 4.

Applicable Section(s)	Description of Change(s)
Synopsis Overview of Study Design; Synopsis Study Population; Synopsis Dosage and Administration; 3.1. Overview of Study Design; 3.2.1. Study Population; 6.1. Screening/Prospective Observational Phase; 9.1.2. Screening/Prospective Observational Phase; Attachment 1	<p>Text regarding antidepressant treatment during the screening/prospective observational phase was revised as follows (bold text added):</p> <p>At the start of the screening/prospective observational phase, the subject must have had documented nonresponse to at least one antidepressant treatment (based on MGH-ATRQ criteria) in the current episode of depression, and the subject is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other ongoing medications being taken for depression at screening (including adjunctive/augmentation therapies) will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4.</p>
Synopsis Overview of Study Design; Synopsis Study Population; 3.1. Overview of Study Design; 3.2.1. Study Population; 6.1. Screening/Prospective Observational Phase; 9.1.2. Screening/Prospective Observational Phase	<p>Text regarding nonresponse to oral antidepressant at end of the screening/prospective observational phase (strikethrough deleted text):</p> <p>Non-response at the end of the screening/prospective observational phase is defined as $\leq 25\%$ improvement in the MADRS total score from Week 1 to Week 4 for 2 consecutive visits and a MADRS total score of ≥ 24 for 2 consecutive visits on Week 2 and Week 4.</p>
16.1. Study-specific Design Considerations	<p>Text regarding subject eligibility was revised as follows (bold text added):</p> <p>For eligibility, subjects must have had nonresponse to at least one prior antidepressant treatment and be currently taking an antidepressant treatment at the start of the screening/prospective observational phase that will be continued as prospective treatment in the screening/prospective observational phase. Only subjects with nonresponse to their current antidepressant treatment after 4 weeks of prospectively observed treatment (for a total duration of antidepressant treatment of at least 6 weeks by the end of the screening/prospective observational phase) will be eligible to proceed to the double-blind induction phase, when all subjects will receive a new oral antidepressant in addition to intranasal esketamine or placebo.</p>
<p>Rationale: The list of key secondary objectives has been revised to exclude several analyses in order to reduce patient burden.</p>	
Synopsis Objectives and Hypothesis; 2.1. Objectives and Hypothesis	<p>The following text have been deleted as indicated and the parameters listed below will not be assessed:</p> <p>Key Secondary Objectives: The key secondary objectives are to assess the effect of intranasal esketamine plus a newly initiated oral antidepressant compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo in the following parameters in elderly subjects with TRD:</p> <ul style="list-style-type: none"> • Functioning and associated disability • Depressive symptoms (subject reported)

Applicable Section(s)	Description of Change(s)
<p>Rationale: Inclusion criterion no. 9 was revised to specify the same requirements for contraception for female partners of male subjects as specified for female subjects.</p>	
4.1. Inclusion Criteria	<p>The text of inclusion criterion no. 9 was revised as follows (bold text added):</p> <p>During the study (ie, from Day 1 of the double-blind induction phase, prior to randomization) and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of intranasal study medication, a man who is sexually active with a woman of childbearing potential</p> <ul style="list-style-type: none"> - must be practicing a highly effective method of contraception with his female partner from those listed above (see examples of highly effective methods of contraception provided for female subjects). - must use a condom if his partner is pregnant. - must agree not to donate sperm. <p>The following text has been deleted: ‘Alternatively female partners of childbearing potential may be practicing a highly effective method of birth control: eg, established use of oral, injected, or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); or male partner sterilization.’</p>
<p>Rationale: The level of education is known to have an impact on the results of the MMSE, with those subjects without a high school education having lower results. The exclusion criterion has been modified to allow for this.</p>	
Synopsis Study Population; 4.2. Exclusion Criteria; 9.7. Other Evaluations	<p>Exclusion criterion no. 11 has been modified as follows (bold text added):</p> <p>Subject has a Mini Mental State Examination (MMSE) <25 or <22 for those subjects with less than an equivalent of a high school education.</p>
<p>Rationale: Exclusion criterion no. 16 was revised to allow prescription use of psychostimulants with dosing restrictions on intranasal treatment session days to allow subjects to safely use at other permitted times during study participation.</p>	
4.2. Exclusion Criteria	<p>Text in exclusion criterion no. 16 was revised as follows (bold text added):</p> <p>Subject has positive test result(s) for drugs of abuse (including barbiturates, methadone, opiates, cocaine, phencyclidine, and amphetamine/methamphetamine) at the start of the screening/prospective observational phase or Day 1 of the double-blind induction phase prior to randomization.</p> <ul style="list-style-type: none"> - Subjects who have a positive test result at screening due to prescribed psychostimulants (eg, amphetamine, methylphenidate, etc.) taken for an indication other than MDD, are permitted to continue to take this medication during the study in accordance with Attachment 1. - Otherwise, subjects who have a positive test result at screening due to prescribed/over-the-counter opiates, or barbiturates—may be permitted to continue in the screening/prospective observational phase if the medication is discontinued at least 1 week or 5 half-lives, whichever is longer, before Day 1 of the double-blind induction phase (prior to randomization) in accordance with Attachment 1 restrictions. The result of the Day 1 (prior to randomization) test for drugs of abuse must be negative for the subject to be randomized.

Applicable Section(s)	Description of Change(s)
Rationale: Clarifications made regarding the usage of antidepressant treatments for indications other than depression during the screening/prospective observational phase, and the use of corticosteroids, psychostimulants, and ADHD medications.	
8. Prestudy and Concomitant Therapy	<p>The following text was added:</p> <p>Any medication that is listed on the MGH-ATRQ and is being taken at the start of the screening/prospective observational phase for an indication other than depression (eg, insomnia) should be continued during the screening/prospective observational phase but must be discontinued before the start of the double-blind induction phase.</p>
Attachment 1	<p>Prohibited Concomitant Medications with Intranasal Study Medication</p> <p>Changes to the text:</p> <p>Antidepressants: “Even if used for other indications other than MDD (eg, trazodone or low dose tricyclic antidepressants for sleep), the use of any medication listed on the ATRQ is not permitted during the treatment phase.”</p> <p>Corticosteroids: changed from “oral” to “systemic”; episodic use permitted (previously prohibited); the following text added: “intermittent IM/IV corticosteroids are permitted (chronic use prohibited)”.</p> <p>Pseudoephedrine: clarified that it is an “orally” administered agent (not intranasal).</p> <p>Psychostimulants: continuous use permitted (previously prohibited); text added “prescribed psychostimulants taken for indications other than MDD can be continued but must not be taken within 12 hours prior to the intranasal treatment session or for 2 hours after the intranasal treatment session”.</p> <p>ADHD medications: continuous use permitted (previously prohibited); text added “Can be continued but must not be taken within 12 hours prior to the intranasal treatment session or for 2 hours after the intranasal treatment session).</p> <p>The following text in the preceding paragraph on prohibited concomitant medications has been revised (text added in bold; strikethrough text deleted):</p> <p>Except where specifically noted, the prohibited medications listed in the following table are prohibited from 1 week (or 5 half-lives, whichever is longer) prior to the first dose of intranasal study medication until after the last dose of intranasal study medication. Note: If a medication is part of the antidepressant treatment regimen being taken at the time of signing the ICF (ie, start of screening/prospective observational phase), dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4. it must be continued unchanged until the end of week 4 of the screening/prospective observational phase.</p>

Applicable Section(s)	Description of Change(s)
<p>Rationale: In the previous Amendment, inclusion of subjects who have thyroid-stimulating hormone (TSH) outside the normal ranges was permitted, however, the text indicating that a subject must have a normal TSH at screening was not removed. This has been corrected in the current Amendment.</p>	<p>4.1 Inclusion Criteria</p> <p>Inclusion criterion no. 7 revised as follows (bold text added):</p> <p>Delete following text: subject “must have thyroid stimulating hormone (TSH) within normal range in the screening/prospective observational phase” and “if the free thyroxine (fT4) is normal, the subject can be enrolled”.</p> <ul style="list-style-type: none"> - Subjects with a pre-existing history of thyroid disease/disorder who are treated with thyroid hormones must be on a stable dosage for 3 months prior to the start of the screening/prospective observational phase. - For any subject (regardless of thyroid history), if the thyroid-stimulating hormone (TSH) value is out of range, a free thyroxine (fT4) will be conducted. If the fT4 value is abnormal and considered to be clinically significant (after discussion with the medical monitor), the subject is not eligible.
<p>Rationale: Provide clarification in the footnotes on antidepressant treatment in the screening/prospective observational phase, and guidance on repetition of the MADRS assessment.</p>	<p>Time and Events Schedule; Screening/Prospective Observational Phase; Double-blind Induction Phase; Footnote a)</p> <p>Footnote a) revised as follows (bold text added):</p> <p>This 3 week period may also be used to optimize medical management if needed to facilitate subject participation. Subjects who do not require a taper and are thus eligible to immediately proceed to the double-blind induction phase can have Visit 1.3 and Visit 2.1 occur on the same day or within 1 week of each other. (If not occurring on the same day, the antidepressant treatment regimen should be continued after Visit 1.3 and then discontinued prior to Visit 2.1).</p> <p>Double-blind Induction Phase; Footnote c)</p> <p>Screening/prospective Observational Phase; Double-blind Induction Phase; Footnote q)</p> <p>Delete “only” from footnote c) that refers to MADRS Visit 2.1 Efficacy Assessment.</p> <p>Footnote q) revised as follows (bold text added, strike through deleted text):</p> <p>The MADRS should be administered no more than 2 days prior to the subject’s targeted (not actual) scheduled clinic visit date (except Visit 2.9, which is within 1 day prior). If performed on the day of the scheduled clinic visit for an intranasal treatment session, the MADRS must be performed prior to the intranasal treatment session.</p>
<p>Rationale: Revise the visit window for Day 28 (Visit 2.9) of the Double-blind Induction Phase to allow more flexibility for conducting the visit.</p>	<p>Time and Events Schedule, Double-blind Induction Phase</p> <p>For Visit 2.9 (Day 28) during the Double-blind Induction Phase, the visit window has been revised to ± 1 day (rather than -1 day).</p>

Applicable Section(s)	Description of Change(s)
	Rationale: Addition of footnote to Time & Events Schedule stating that information on adverse events and concomitant therapies will be requested by site staff during the Follow-up Phase by remote assessment.
Time and Events Schedule, Follow-up Phase	The following statement was added as a footnote (e) to the remote assessment (Visit 3.1) of the follow-up phase: For the Remote Assessment (RA) Visit 3.1, site staff will contact the subject by telephone to obtain information regarding adverse events and concomitant therapies
	Rationale: Removal of requirement to report arterial oxygen saturation <93% and any treatment-emergent change in the nasal examination as adverse events because adverse event reporting in these instances should be at the discretion of the PI.
9.6. Safety Evaluations	Text revised as follows (bold text added): The following statement was deleted from reporting arterial oxygen saturation: Any arterial oxygen saturation <93% “and lasting for more than 2 minutes“...”will be reported as an adverse event” Text now states: “Any arterial oxygen saturation <93% should be confirmed by an additional measurement on another part of the body”. The following statement was deleted from the description of nasal examinations: “Any treatment-emergent change or worsening from the baseline examination will be recorded as an adverse event”.
	Rationale: Removal of LSD and MDMA from urine drug screen results that will lead to discontinuation as LSD is not measured in the current urine drug screen and prescribed psychostimulants are now permitted.
4.3. Prohibitions and Restrictions	Lysergic acid diethylamide (LSD) and MDMA were deleted from the list of drugs that will lead to discontinuation if detected in the urine drug screen during the study.
	Rationale: Clarification of procedure to follow if subjects wish to withdraw from the study.
10.2 Withdrawal from the Study	<u>Withdrawal of Consent</u> : the following text has been revised (bold text added): Subjects who wish to withdraw from the study should be asked if they are agreeable to continue to an early withdrawal visit (if withdrawing from the double-blind induction phase) and the follow up phase, or to be contacted to collect follow-up information.
	Rationale: Added definition of treatment-resistant depression (TRD) to the synopsis.
Synopsis Study Population	Definition of TRD from Section 3.2.1 also added to the synopsis under Study Population. ‘Treatment-resistant depression (TRD) is defined as a lack of clinically meaningful improvement after treatment with at least 2 different antidepressant agents prescribed in adequate dosages for adequate duration.’

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of adverse event reporting procedures in the instance of pregnancy. In addition, clarification that all SAEs must be reported using the SAE form.	
12.3.1. All Adverse Events	Text revised as follows (bold text added): <ul style="list-style-type: none"> The text stipulating 30 days for reporting serious adverse events has been deleted. <p>All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety), with the exception of pregnancy which will be reported up to 6 weeks after the last dose of study medication (females) or 90 days after the last dose of study medication (partners of male participants). Serious adverse events, including those spontaneously reported to the investigator, to within 30 days after the last dose of study drug must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.</p>
Rationale: Minor changes were made throughout the protocol for compliance with updated protocol template text and to correct errors.	
9.3. Pharmacokinetics	To correct an error, the text was revised to change “serum” to “plasma”: Plasma collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period.
17.5 Case Report Form Completion	Delete text stating “All data relating to the study must be recorded in CRF.”
References	Removed edition number and date from reference 42. Removed original reference number 49 and 86 from the list and updated the reference list.
Investigator Agreement Page	Removed the “LAST PAGE” designation.

Amendment INT-2 (10 January 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to update and/or clarify protocol content based on ongoing feedback received during study initiation activities.

Applicable Section(s)	Description of Change(s)
Rationale: Indicate that a subject will be excluded if the subject’s depressive symptoms have previously demonstrated nonresponse to esketamine or ketamine in the current major depressive episode.	
Synopsis, Study Population; 4.2. Exclusion Criteria	Exclusion criterion no.1 has been revised to state that potential subjects will be excluded if the subject’s depressive symptoms have previously demonstrated nonresponse to “esketamine or ketamine in the current major depressive episode, per clinical judgment”. The following criterion for exclusion has been deleted: “Any subjects who have previously received esketamine or ketamine for depression.”

Applicable Section(s)	Description of Change(s)
	Rationale: Clarify that “at least 7 treatments with unilateral ECT” (electroconvulsive therapy) encompasses bilateral as well as unilateral ECT treatments.
Synopsis, Study Population; 4.2. Exclusion Criteria	Exclusion criterion no.1 now states “unilateral/bilateral” rather than only “unilateral.”
	Rationale: Indicate that subjects who received vagal nerve stimulation in the current depressive episode are excluded.
Synopsis, Study Population; 4.2. Exclusion Criteria	Exclusion criterion no. 2 was revised to now exclude a subject who has received vagal nerve stimulation (VNS) in the current depressive episode. It previously stated subjects with a vagal nerve implant were excluded.
	Rationale: Clarification of the description of major depressive disorder (MDD) and obsessive compulsive disorder in the exclusion criteria.
Synopsis, Study Population; 4.2. Exclusion Criteria	The text of exclusion criterion no.3. was modified: <ul style="list-style-type: none"> • “MDD with psychosis” was revised to “MDD with psychotic features” • Only Subjects with “current” obsessive compulsive disorder will be excluded.
	Rationale: Clarification of the conditions for exclusion of subjects with coronary artery disease.
4.2. Exclusion Criteria	The text of exclusion criterion no.8. was modified such that the following cardiovascular conditions will now be excluded: <ul style="list-style-type: none"> • Coronary artery disease with myocardial infarction, unstable angina, or revascularization procedure (eg, coronary angioplasty or bypass graft surgery) within 12 months before the start of the screening/prospective observational phase. Subjects who have had a revascularization performed >12 months prior to screening and are clinically stable and symptom-free, per investigator’s clinical judgment, can be included.
	Rationale: Clarification of the wording used for describing a subject’s antihypertensive medication.
4.2. Exclusion Criteria	The text of exclusion criterion no. 9 was revised to now state “antihypertensive medication(s)” rather than “antihypertensive medication regimen.”
	Rationale: Clarification of definition of clinically significant ECG abnormalities as defined by QT interval corrected according to Fridericia’s formula (QTcF).
4.2. Exclusion Criteria	Exclusion criterion no.13 has been revised as follows. The first subbullet in exclusion criterion no. 13 was separated into two subbullets (bold text was added): <ul style="list-style-type: none"> • During screening, a QT interval corrected according to Fridericia's formula (QTcF) (ms): ≥ 450 ms; if the QTcF is prolonged on the initial ECG, the average QTcF of three ECGs, recorded at least 4 minutes apart, must not be ≥ 450 ms. • On Day 1 (predose), a QT interval corrected according to Fridericia's formula (QTcF): ≥ 450 ms based on the site-evaluated ECG; if the QTcF is prolonged on the initial ECG, the average QTcF of three ECGs, recorded at least 4 minutes apart, must not be ≥ 450 ms. <p>In the second subbullet, the bold text was added as shown below:</p> <ul style="list-style-type: none"> • Evidence of 2nd and 3rd degree AV block, or 1st degree AV block with PR interval >200 ms (if the initial PR interval is <240 ms, may repeat the ECG once and use average of both readings), complete left bundle branch block (LBBB), or complete right bundle branch block (RBBB).

Applicable Section(s)	Description of Change(s)
	Rationale: The use of concomitant medications that prolong the QT interval/corrected QT (QTc) are no longer excluded as there is no known QTc increase signal known with esketamine and extensive ECG monitoring is in place and precautions in case of increase in QTc are added.
4.2. Exclusion Criteria	Exclusion criterion no. 14 has been revised as follows: Subject has a history of additional risk factors for Torsades des Pointes (eg, heart failure, hypokalemia, family history of Long QT Syndrome), or the use of concomitant medications that prolong the QT/QTc interval.
	Rationale: Indicate that the screening test for abnormal ALT and AST may be repeated once during screening if there is an explanation for a transient out of range value.
4.2. Exclusion Criteria	Text was added to exclusion criterion no. 15 to specify that a repeat of the screening test for abnormal ALT and AST is permitted once during the screening period, per investigator discretion, provided there is an explanation for a transient out of range value.
	Rationale: Clarification that a positive test for cannabinoids on Day 1 is exclusionary, but not at screening.
4.2. Exclusion Criteria	Text of exclusion criterion no. 16 was revised to clarify that a positive test for cannabinoids at the start of the screening/prospective phase is not exclusionary; however, a positive test for cannabinoids on Day 1 (predose) of the double-blind-treatment phase is exclusionary.
	Rationale: The term “secondary diabetes” was removed from exclusion criterion no. 18 because the criterion states that any uncontrolled diabetes mellitus is exclusionary.
4.2. Exclusion Criteria	The text of exclusion criterion no. 18 was modified to delete the phrase “or secondary diabetes”.
	Rationale: Provide clarification that the investigator’s clinical judgment based on assessment will be used to determine eligibility of subjects who have any anatomical or medical condition that may impede delivery or absorption of intranasal study drug.
4.2. Exclusion Criteria	The text of exclusion criterion no. 20 was modified to indicate that the “investigator’s clinical judgment based on assessment” will be used to determine eligibility. Redundant text (ie, examples of structural or functional abnormalities) has been deleted.
	Rationale: Exclusion criterion no. 21 is no longer required as it is covered as part of exclusion criterion no. 20.
4.2. Exclusion Criteria	The text of exclusion criterion no. 21 has been deleted.
	Rationale: Clarify that a subject with obstructive sleep apnea can be included if the subject receives effective treatment/therapy, which results in an apnea-hypopnea index of <30.
Synopsis, Study Population; 4.2. Exclusion Criteria	<ul style="list-style-type: none"> The text of exclusion criterion no. 25 has been modified as follows (bold text added): “Subject has a score of ≥ 5 on the STOP-Bang questionnaire, in which case obstructive sleep apnea must be ruled out (eg, apnea-hypopnea index [AHI] <30). A subject with obstructive sleep apnea can be included if he or she is using a positive airway pressure device or other treatment/therapy that is effectively treating (ie, AHI <30) his or her sleep apnea.” In the list of exclusion criteria in the synopsis (Study Population), the text “STOP-Bang questionnaire score of ≥ 5” has been deleted as this is not necessarily an exclusion per exclusion criterion no. 25.

Applicable Section(s)	Description of Change(s)
	<p>Rationale: Clarify that a subject is excluded if the subject has participated in 2 or more interventional studies (for a psychiatric condition) with different investigational drugs, or the subject is enrolled in an investigational study, which is interventional.</p>
4.2. Exclusion Criteria	<p>The text of exclusion criterion no. 26 has been modified as follows (bold text added): “Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 60 days before the start of the screening/prospective observational phase, or has participated in 2 or more MDD or other psychiatric condition clinical interventional studies (with different investigational drugs including investigational vaccines or investigational medical devices for each study) in the previous 1 year before the start of the screening/prospective observational phase, or is currently enrolled in an investigational interventional study.”</p>
	<p>Rationale: Subjects with severe renal impairment (creatinine clearance <30 ml/min) are being excluded (exclusion criterion no. 31) as a safety precaution, since the effect of impaired renal clearance on the pharmacokinetics of intranasal esketamine is not fully known and subjects may be more vulnerable to blood pressure increases.</p>
4.2. Exclusion Criteria	<p>Exclusion criterion no. 31 for all subjects was added: “Severe renal impairment (creatinine clearance <30 ml/min).”</p>
	<p>Rationale: Clarification added to inclusion criterion regarding nonresponse to oral antidepressant treatments in current episode of depression.</p>
Synopsis, Overview of Study Design, Study Population, Dosage and Administration; 3.1. Overview of Study Design; 3.2.1. Study Population; 4.1. Inclusion Criteria; 6.1. Screening/Prospective Observational Phase; 9.1.2. Screening/Prospective Observational Phase	<p>The text of inclusion criterion no. 3 was modified to state that the subject must:</p> <ul style="list-style-type: none"> • Have had nonresponse ($\leq 25\%$ improvement) to ≥ 2 but ≤ 5 (if current episode is > 2 years, upper limit applicable to only the last 2 years) oral antidepressant treatments in current episode of depression. • Have had nonresponse confirmed by documented records (eg, medical/pharmacy/prescription records, a letter from treating physician, etc.). • Be taking one of the oral antidepressant treatment(s) with nonresponse that is documented on the MGH-ATRQ (ie, oral antidepressant treatment must be taken for at least 6 weeks at the minimum therapeutic dose with a lack of clinically meaningful improvement) at the start of the screening/prospective observational phase. <p>The following text was added to specify the criteria for non-response at the end of the screening/observational phase: “Non-response at the end of the screening/prospective observational phase is defined as $\leq 25\%$ improvement in the MADRS total score for 2 consecutive visits and a MADRS total score of ≥ 28 for 2 consecutive visits.”</p> <p>Other sections of the text were revised to correspond to the changes in the inclusion criterion.</p>
	<p>Rationale: Indicate that the severity of a subject’s depressive symptoms in the current major depressive episode must also be confirmed using a Site Independent Qualification Assessment.</p>
Synopsis, Study Population; 3.2.1. Study Population; 4.1. Inclusion Criteria; 9.1.2. Screening/Prospective Observational Phase	<p>The text of inclusion criterion no. 5 was modified as follows (bold text added): “The subject’s current major depressive episode, depression symptom severity (Week 1 MADRS total score ≥ 28 required), and antidepressant treatment response in the current depressive episode, must be confirmed using the Site Independent Qualification Assessment.”</p> <p>Other sections of the text were revised to correspond to the changes in the inclusion criterion.</p> <p>Text was added in Section 3.2.1 (Study Population) indicate that the severity of a subject’s depressive symptoms must be confirmed using a Site Independent Qualification Assessment.</p>

Applicable Section(s)	Description of Change(s)
Rationale: Clarify text in inclusion criterion regarding additional lab test for assessing levels of free thyroxine.	
4.1. Inclusion Criteria; 9.1.1 Overview, Table 5; 9.6 Safety Evaluations	<p>Text was added to inclusion criterion no. 7 to clarify that for any subject (regardless of thyroid history), if the TSH value is out of range, a free thyroxine (fT4) will be conducted. If the fT4 is normal, the subject can be enrolled. If the fT4 value is out of range, the subject is not eligible.</p> <p>The following statements were deleted from inclusion criterion no. 7:</p> <ul style="list-style-type: none"> For those without a pre-existing history of hypothyroidism, a normal thyroid-stimulating hormone [TSH] is required at screening. If the TSH is below the normal range, free thyroxine (fT4) levels will be measured and if fT4 is within the normal range the subject can be enrolled. <p>Other sections of the text were revised to correspond to the changes in the inclusion criterion.</p> <p>Row was added to Table 5 in Section 9.1.1 (Overview) to specify the volume of blood per sample used to assess levels of fT4, and footnote 'e' was added to this table to specify that for any subject (regardless of thyroid history), if the TSH value is out of range, a free thyroxine will be conducted.</p>
Rationale: The text in inclusion criterion no. 9 was revised to clarify the description of methods of birth control for a man who is sexually active with a woman of childbearing potential or a woman who is pregnant.	
4.1. Inclusion Criteria	<p>The text of inclusion criterion no. 9 was modified as follows (bold text was added):</p> <p>A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository from Day 1 of the double blind induction phase (prior to randomization) through 3 months after the last dose of intranasal study medication. During the study (ie, from Day 1 of the double-blind induction phase, prior to randomization) and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of intranasal study medication, in addition to the user independent highly effective method of contraception, a man</p> <ul style="list-style-type: none"> who is sexually active with a woman of childbearing potential must agree to use a double-barrier method of contraception (eg, diaphragm or cervical/vault caps plus condom with spermicidal foam/gel/film/cream/suppository) who is sexually active with a woman who is pregnant must use a condom must agree not to donate sperm. <p>Alternatively female partners of childbearing potential may be practicing a highly effective method of birth control: eg, established use of oral, injected, or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); or male partner sterilization.</p> <p>Note: If the female partner's childbearing potential changes after start of the study, a the female partner of a male study subject, must begin a highly effective method of birth control, as described above.</p>
Rationale: Correct a statement referring to the US prescribing information for duloxetine.	
1.2.2.1. Duloxetine	<p>The phrase "Although not in the US prescribing information" was deleted from the statement regarding evaluation of an initial dose of 30 mg/day as the US prescribing information for duloxetine does indicate that for some patients, it may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily.</p>

Applicable Section(s)	Description of Change(s)
	Rationale: Text added to provide the details of predose procedures to be followed in the event an intranasal treatment session is postponed/delayed (within the visit window) due to a predose vital sign assessment.
Time & Events Schedule; 9.6. Safety Evaluations	Text was added in the description of safety evaluations to indicate that if an intranasal treatment session is postponed/delayed (within the visit window) due to a predose vital sign assessment, all time points of the following assessments must be repeated on the actual intranasal treatment session day: vital signs, 12-lead ECG, C-SSRS, MOAA/S, pulse oximetry, BPRS+, and CADSS. In the Time & Events Schedule (Screening/prospective Observational Phase and Double-blind Phase), the text of footnote 'o' was revised for consistency with the text added in the description of safety evaluations, and footnote 'o' was deleted from the row for CGADR assessment.
	Rationale: MADRS total score is to be recorded at Study Day 22 (Visit 2.7); however, in the Time & Events Schedule the MADRS assessment was mistakenly omitted at this timepoint.
Time & Events Schedule	The Time & Events Schedule (Screening/prospective Observational Phase and Double-blind Phase) was revised to indicate that the MADRS total score is to be recorded at Study Day 22 (Visit 2.7).
	Rationale: The row in the Time and Events Schedule showing assessment windows for the MADRS was removed due to misunderstandings it was creating relative to the visit windows.
Time & Events Schedule	In the Time & Events Schedule (Screening/prospective Observational Phase and Double-blind Phase), the row for "Remote MADRS interview window" was deleted, and the following guidance regarding MADRS assessment windows was added to footnote 'q': "The MADRS should be administered no more than 2 days prior to the subject's scheduled clinic visit. If performed on the day of the scheduled clinic visit for an intranasal treatment session, the MADRS must be performed prior to the intranasal treatment session."
	Rationale: Text revised to clarify the arterial oxygen saturation level that requires further monitoring.
9.6. Safety Evaluations	Text regarding pulse oximetry measurement was corrected to indicate that postdose oxygen saturation levels <93% (not ≤93%) require further monitoring.
	Rationale: Clarification of intranasal esketamine dose adjustments which are permitted after Day 15 for consistency.
3.2.4 Treatment Groups and Dose Selection	The text in the Intranasal Study Drug section has been revised to clarify that the intranasal esketamine dose may be decreased by 28 mg after Day 15, while increases in esketamine dose are not permitted after Day 15 (for consistency with Section 6.2, Table 4).
	Rationale: Remove restriction regarding up-titration in dose during the double-blind induction phase for subjects who had a previous down-titration in dose due to elevated blood pressure.
Synopsis, Dosage and Administration; 6.2 Double-blind Induction Phase	The following sentence has been deleted from the text "No up-titration in dose is permitted during the double-blind induction phase if there was a prior down titration due to elevated blood pressure."
	Rationale: Clarification of the description for the Hopkins Verbal Learning Test-Revised (HVLT-R) recall test.
Time & Events Schedule; 9.6. Safety Evaluations	Text regarding cognition testing has been revised to clarify the description of the HVLT-R recall text and to add text indicating that subjects will complete a practice session for the computerized cognitive battery, but not the HVLT-R, during the screening/prospective observational phase.

Applicable Section(s)	Description of Change(s)
	<p>Rationale: Indicate that biomarkers will be assessed at the protein and RNA level and provide the rationale for recommendation of subject adherence to a low fat diet on the day of sample collection.</p>
Synopsis, Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations; 3.2.9. Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations	<p>Text was added to specify that biomarkers will be assessed at both the protein and RNA level.</p> <p>In addition, the following sentence was added: “On the day of biomarker sample collection, it is preferred that subjects adhere to low fat diet (as an alternative to fasting) to reduce the level of postprandial lipemia in blood samples because moderately or grossly lipemic specimens may interfere with assay results.”</p>
	<p>Rationale: Blood volume table updated to include changes in blood volumes for biomarker (protein/DNA) assessment.</p>
9.1.1. Overview, Table 5	<p>Table 5 was revised as follows:</p> <ul style="list-style-type: none"> • Volume of blood sample for Biomarker: protein was changed from 13 mL to 10 mL. • Volume of blood sample for Biomarker: DNA was changed from 8.5 mL to 6 mL • Total Volume of Blood to be collected per subject was changed from 125.5 mL to 112.0 mL. • Deleted footnote ‘d’ Blood volume listed under protein biomarkers represents the combined volume of several different collection tubes. • In Double-blind Induction Phase section of the table, merged the two rows for ‘Biomarker: protein visits’ to a single row. Description now states: “Biomarker: protein (at Visits 2.1, 2.3, and 2.8). The volume of sample collected at each visit is 10 mL, and the number of samples per subject was revised to 3.
	<p>Rationale: Clarification of guidance on blood pressure monitoring on intranasal treatment session days, including clarification that discontinuation is mandatory for subjects who meet blood pressure criteria on intranasal treatment session days for discontinuation from further dosing.</p>
6.2.1. Guidance on Blood Pressure Monitoring on Intranasal Treatment Session Days	<p>In the heading for the section, the term “Dosing Days” has been replaced with “Intranasal Treatment Session Days”.</p> <p>The following revisions were made to clarify guidance on blood pressure monitoring on intranasal treatment session days (bold text was added):</p> <p>“Given the potential for treatment emergent transient elevation in systolic and diastolic blood pressure, the following guidance should be followed on intranasal dosing days:</p> <ul style="list-style-type: none"> • If subsequent to fulfilling the inclusion and exclusion criteria on Day 1 (ie, applicable for all other intranasal treatment session days after Day 1), a subject’s pre-dose SBP is ≥ 150 mmHg and/or DBP is ≥ 90 mmHg, it is recommended that to repeat the blood pressure measurement is repeated after the subject rests for 10 minutes in sitting or recumbent position. If after rest and repeated measurements, the pre-dose SBP is ≥ 150 mmHg and/or the DBP is ≥ 90 mmHg, then dosing should be postponed and the subject scheduled to return on the following day or within the given visit window. If the blood pressure elevation still persists on the next visit, the subject will be scheduled for a consultation by cardiologist, other specialist, or a primary care physician; prior to further dosing. • If at any postdose time point on the dosing day the SBP is ≥ 180 mm Hg but < 190 mm Hg and/or the DBP is ≥ 100 mm Hg but < 110 mm Hg, further intranasal dosing should be interrupted and the subject should be referred to a cardiologist, other specialist, consultation or primary care physician for a follow-up assessment. <ul style="list-style-type: none"> – After the assessment by a cardiologist, other specialist, or primary care physician, if recommended by the referring doctor and provided considered appropriate according to the clinical judgment of the investigator for the subject is given approval to continue in the study, the subject may continue with intranasal dosing if the pre-dose blood pressure at the next scheduled

Applicable Section(s)	Description of Change(s)
Synopsis, Dosage and Administration; 6.2. Double-blind Induction Phase	<p>visit is within the acceptable range (see bullet above).</p> <ul style="list-style-type: none"> • If at any postdose time point on the a dosing day the SBP is ≥ 190 mm Hg and/or the DBP is ≥ 110 mm Hg, the subject shouldmust discontinue from further dosing and be referred to a cardiologist, other specialist, or primary care physician for a follow-up assessment. • During the double-blind induction phase, at 1.5 hours postdose, if the SBP is ≥ 160 mm Hg and/or the DBP ≥ 100 mm Hg, assessments should continue every 30 minutes until: <ul style="list-style-type: none"> – the blood pressure is < 160 mm Hg SBP and < 100 mm Hg DBP, or – in the investigator’s clinical judgment, the subject is clinically stable and can be discharged from the study site, or – until the subject is referred for appropriate medical care if clinically indicated. <p>If the blood pressure remains ≥ 180 SBP and/or ≥ 110 mmHg DBP 2 hours after dosing, the subject should be referred for immediate medical treatment.</p> <p>For consistency with exclusion criterion no. 9, the blood pressure requirements in the instructions for intranasal dosing were revised to state “Prior to intranasal dosing, subjects must not have a blood pressure > 150 mm Hg systolic and/or > 90 mm Hg diastolic” instead of “Prior to intranasal dosing, subjects must have a blood pressure $\leq 150/90$ mm Hg.”</p>
Rationale:	Alert site staff to ECG readings that would raise safety concerns and necessitate subject withdrawal and study discontinuation.
9.6. Safety Evaluations	<p>The following text was added in the Single, 12-lead ECG section: The subject must be discontinued at any time point after baseline (Day 1, predose) if:</p> <ul style="list-style-type: none"> • QTcF change from baseline is ≥ 60 ms AND QTcF > 480 ms, or • QTcF > 500 ms.
10.2. Withdrawal from the Study	<p>The following bullet was added to the list of reasons for withdrawal from the study:</p> <ul style="list-style-type: none"> • At any time point after baseline (Day 1, predose), the subject has a: <ul style="list-style-type: none"> – QTcF change from baseline ≥ 60 ms AND QTcF > 480 ms, or – QTcF > 500 ms
Rationale:	Provide further clarification regarding how the current regimen should remain unchanged for the duration of the screening/prospective observational phase and provide the criterion for non-response at the end of the screening/prospective observational phase (ie, site investigators are no longer blinded).
Synopsis, Overview of Study Design, Study Population, Dosage and Administration; 3.1. Overview of Study Design; 3.2.1. Study Population; 6.1. Screening/Prospective Observational Phase; 9.1.2. Screening/Prospective Observational Phase	<p>Text was revised to clarify that:</p> <ul style="list-style-type: none"> • At the start of the screening/prospective observational phase the subject’s antidepressant treatment, as well as any ongoing medications for depression (including adjunctive and augmentation therapies), will continue unchanged at the same dosage from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase. • During the screening/prospective observational phase, subjects taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening/prospective observational phase can continue these medications, but no dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the screening/prospective observational phase. • Eligible subjects who do not require a tapered discontinuation of their antidepressant treatment(s) can proceed immediately into the double-blind induction phase. • Non-response at the end of the screening/prospective observational phase is defined as $\leq 25\%$ improvement in the MADRS total score for 2 consecutive visits and a MADRS total score of ≥ 28 for 2 consecutive visits.

Applicable Section(s)	Description of Change(s)
Rationale: Provide clarification that all medication(s) being used for depression must be discontinued after completion of the 4-week prospective observational phase.	
Synopsis, Overview of Study Design, Dosage and Administration; 3.1. Overview of Study Design; 3.2.2. Study Phases; 6.1. Screening/Prospective Observational Phase; 9.1.2. Screening/Prospective Observational Phase	Text was revised to clarify that eligible subjects who enter the double-blind phase will discontinue all of their current medication(s) being used for antidepressant treatment, including adjunctive/augmentation therapies.
Rationale: Indicate that during the double-blind induction phase dosing of the oral antidepressant is to follow the mandatory titration schedule and doses of oral antidepressant study medication are not to exceed the maximum dose defined in the titration schedule.	
Synopsis, Dosage and Administration; 3.2.4. Treatment Groups and Dose Selection; 6.2 Double-blind Induction Phase; 9.1.3. Double-blind Induction Phase	<ul style="list-style-type: none"> Deleted text stating that dosing of the oral antidepressant during the double-blind induction phase will follow the local prescribing information, with a forced titration to the maximum tolerated dose. Added text stating that dosing of the oral antidepressant during the double-blind induction phase will follow a mandatory titration schedule (provided in Attachment 3). Statement added to indicate that during the double-blind induction phase, doses of oral antidepressant study medication are not to exceed the maximum dose defined in the titration schedule.
Attachment 3	The following statement was deleted from the first paragraph: "Adjustments to the titration schedule may be required in other countries in order to conform to local prescribing information."
Rationale: Update and clarification to prohibited medications and substances and restrictions during the double-blind induction phase.	
Synopsis, Overview of Study Design; 3.1. Overview of Study Design; 4.3. Prohibitions and Restrictions	The following text was added to the list of Prohibitions and Restrictions: "Subjects taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening/prospective observational phase can continue these medications during the induction phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the induction phase, with the exception of the use of permitted benzodiazepine rescue medication. Benzodiazepines and non-benzodiazepine sleeping medication (eg, zolpidem, zaleplon, eszopiclone, and ramelteon) are prohibited within 12 hours prior to the start of each intranasal treatment session or cognition testing."
4.3. Prohibitions and Restrictions	Lysergic acid diethylamide (LSD) was added to the list of drugs that will lead to discontinuation if detected in the urine drug screen from Day 1 of the induction phase through the final visit in the double-blind induction phase.
4.3. Prohibitions and Restrictions	Removed restriction stating that subjects should not ingest grapefruit juice, Seville oranges, or quinine for 24 hours before intranasal dosing.

Applicable Section(s)	Description of Change(s)
Rationale: Clarifications for the use of prestudy and concomitant therapies.	
4.3. Prohibitions and Restrictions; 8. Prestudy and Concomitant Therapy	Clarified that psychotherapy includes cognitive behavioral therapy (CBT); subjects receiving CBT must have had therapy ongoing for the last 3 months prior to the screening/prospective observation phase; new CBT is prohibited, but new psychotherapy is allowed; and any change in existing therapy or new therapy must be documented on the concomitant therapies form.
8. Prestudy and Concomitant Therapy	Added that antidepressant treatments which are not listed on the MGH-ATRQ but were used or are currently being used as antidepressant treatment in the current depressive episode must be recorded on the 'Concomitant Therapy' eCRF.
8. Prestudy and Concomitant Therapy	Clarified note regarding the timing of oral antihypertensive medications relative to administration of intranasal study drug.
8. Prestudy and Concomitant Therapy	Clarified that unless clinically indicated, it is recommended that transient increases in blood pressure not be treated.
Rationale: Clarifications to Attachment 1 regarding prohibited concomitant medications.	
Attachment 1	<p>The following changes were made in Attachment 1 describing prohibited concomitant medications with intranasal study medication (esketamine or placebo):</p> <ul style="list-style-type: none"> • Included the following statement preceding the table listing prohibited medications: "Note: If a medication is part of the antidepressant treatment regimen being taken at the time of signing the ICF (ie, start of screening/prospective observational phase), it must be continued unchanged until the end of Week 4 of the screening/prospective observational phase. If the investigator determines it is clinically appropriate, the antidepressant medication may be tapered during the optional, up to 3-week, taper period". • Deleted row referring to CYP3A4 inhibitors as prohibited concomitant medication. • Added a new row for prohibited non-stimulant ADHD medications (eg, atomoxetine, guanfacine). • Added new text to comments on the use of antidepressants in this study, stating that "Even if used primarily for sleep, trazodone or low dose tricyclic antidepressants are not permitted during the treatment phase".
Attachment 1	<ul style="list-style-type: none"> • Deleted text in comments on the use of non-benzodiazepine sleeping medication. • Added phrase "(at dosages less than or equal to the equivalent of 6 mg/day of lorazepam)" to describe benzodiazepines in the "Drug Class" column for consistency with the text in other sections. • Provided additional examples of anorexiant (phendimetrazine) that are prohibited as concomitant medication for reasons of safety, anticonvulsants (pregabalin) that are permitted when used for indications other than seizures, and psychostimulants (methylphenidate, modafinil, armodafinil) that are prohibited due to cardiovascular safety. • Added row for non-vitamin K antagonist oral anticoagulant agents (eg, dabigatran, rivaroxaban, apixaban). • Added statement indicating that pseudoephedrine-containing products should not be used within 12 hours prior to an intranasal treatment session. • Added "Safety and PD interaction" as reason for prohibitions listed for cough/cold preparations/nasal solutions containing vasoconstrictors, decongestants. • The comment regarding thyroid hormone supplements was deleted as it was not consistent with the text in inclusion criterion no. 7.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of criteria for subject withdrawal.	
10.2 Withdrawal from the Study	<p data-bbox="483 268 1312 300">Text pertaining to subject withdrawal from the study was clarified as follows:</p> <ul data-bbox="483 300 1443 989" style="list-style-type: none"> <li data-bbox="483 300 1443 457">• Added the following text to the “Withdrawal of Consent” bullet: “(Note: See “Withdraw of Consent” section below; this should only be selected as a reason for withdrawal if the subject does not agree to any further study assessments or procedures. If the subject is agreeable to participating in the Early Withdrawal visit and the follow-up phase, another reason for withdrawal should be selected.)” <li data-bbox="483 457 1443 520">• Added text to specify that if the subject withdraws from the study before the end of the double-blind induction phase, an Early Withdrawal visit is to be performed. <li data-bbox="483 520 1443 800">• Added text to detail efforts study personnel must make to contact subjects to determine the reason for discontinuation/withdrawal: “This should include at least 3 telephone calls, certified letters, email requests, etc. To ensure access to follow-up subjects, the study sites should attempt to obtain both primary and secondary telephone contact numbers (eg, home, work, and mobile phone numbers including phone numbers of relatives), as well as other contact information (eg, e-mail addresses) from subjects before randomization. In addition, the study site should emphasize the importance of follow-up information to the subject before randomization.” <li data-bbox="483 800 1443 831">• Added text to indicate that subjects who withdraw will not be replaced. <li data-bbox="483 831 1443 989">• The following text was deleted: “Study drug assigned to the withdrawn subject may not be assigned to another subject. If a subject withdraws from the study before the end of the double-blind induction phase for reasons other than withdrawal of consent, an early withdrawal visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase.”
10.2 Withdrawal from the Study	<ul data-bbox="483 1010 1443 1577" style="list-style-type: none"> <li data-bbox="483 1010 1443 1577">• Added the following text under a separate heading (“Withdrawal of Consent”) to specify the conditions and procedures for withdrawal due to “withdrawal of consent”: <p data-bbox="540 1104 1443 1199">“Every effort will be made in the study to ensure withdrawal of consent is not selected as a reason for discontinuation when in fact the subject withdrew for an identifiable reason (eg, due to an adverse event or lack of efficacy). Subjects who wish to withdraw from the study should be asked if they are agreeable to be contacted to collect follow-up information. Subjects who are not agreeable to follow-up contact will be withdrawn from the study as “withdrawal of consent.” Subjects who no longer wish to take study drug but agree to provide follow-up information will be withdrawn from the double-blind induction phase with the reason noted as “Other” and will specify the reason why. For a subject who withdraws consent, it is recommended that the subject withdraw consent in writing; if the subject refuses or is physically unavailable, the study site should document and sign the reason for the subject’s failure to withdraw consent in writing and maintain it with the subject’s source records. The investigator will be responsible for making all required notifications to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).”</p>
10. Subject Completion/Withdrawal; 16.2.5. Long-Term Retention of Samples for Additional Future Research	<p data-bbox="483 1598 1443 1692">Added a separate heading (10.3 Withdrawal From the Use of Samples in Future Research) for description of withdrawal from the use of research samples. The text in this section has not been changed.</p>

Applicable Section(s)	Description of Change(s)
Rationale: A diary has been added to record oral antidepressant use, and information regarding oral antidepressant use and accountability has been clarified.	
Synopsis, Dosage and Administration; Time & Events Schedule; 6.2. Double-Blind Induction Phase; 7. Treatment Compliance; 15. Study-Specific Materials	<p>The following changes were made:</p> <ul style="list-style-type: none"> Text added to indicate that a diary will be provided for subjects to keep a record of oral antidepressant study medication use, to be reviewed and updated (if applicable), and returned at the end of the double-blind induction phase, in the event of an early withdrawal, or at the end of the follow-up phase. Text regarding the timing of oral antidepressant medication administration has been revised to now state: "On intranasal dosing days, it is recommended the oral antidepressant medication not be taken until at least 3 hours after the intranasal treatment session." Row in the Time & Events Schedule (Screening/prospective Observational Phase and Double-blind Phase) for "Additional supply of oral antidepressant" has been deleted and the information has been added to the row "Dispensing of new oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR)". Text revised to indicate that antidepressant treatment adherence will be assessed by performing pill counts (ie, compliance check) and drug accountability during the follow-up phase as well as the double-blind induction phase.
Rationale: Provide further clarification regarding site staff training requirements for intranasal treatment sessions.	
Synopsis, Dosage and Administration; 6.2. Double-blind Induction Phase	Text revised to state that a site staff member with training in cardiopulmonary resuscitation (eg, Basic Life Support course or equivalent courses) that is up to date per local regulations must be present with the subject during the intranasal treatment sessions and the postdose observation period.
Rationale: Update list of study-specific materials	
15. Study-Specific Materials	Guidance document for the use of the MGH-ATRQ has been added.
Rationale: Clarification of study site personnel availability for on-site monitoring visits.	
17.8. Monitoring	Text revised to now state: "It is expected that study-site personnel will be available to provide an update on the progress of the study at the study site." Minor revisions were also made to clarify the description of source documents and the comparison of recorded data with source data.
Rationale: Clarification of the content of data in the electronic case report form (eCRF)	
17.11. Use of Information and Publication	Text revised to now stipulate that the Clinical Study Report generated by the sponsor will contain eCRF data from all study sites that participated in the study and will represent uploaded data transferred from external service providers into the sponsor's database.
Rationale: Include published data relating to adverse events associated with use of esketamine.	
1.1.2.3. Safety and Tolerability	Additional text added to include published data relating to adverse events associated with short-term use of esketamine.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of text regarding oral antidepressant medication use in the follow-up phase	
Synopsis, Overview of Study Design; Dosage and Administration; Time & Events Schedule; 3.1. Overview of Study Design; 6.3. Follow-up Phase; 9.1.3. Double-blind Induction Phase; 9.1.4. Follow-up Phase	Text revised to now state that following the 4-week double blind treatment phase, the oral antidepressant medication should be continued for the 2 weeks of the follow-up phase unless determined as not clinically appropriate.
Rationale: Clarification of the language regarding subjects who develop treatment emergent ulcerative cystitis to indicate the discontinuation of such subjects is mandatory.	
3.2.6 Safety Evaluations; 9.6. Safety Evaluations	Updated/ added text in these sections describing the BPIC-SS and instructions for discontinuing due to ulcerative cystitis, to read as follows: "If a subject is determined to have a diagnosis of ulcerative cystitis the subject must be discontinued from the study and followed up with appropriate medical care."
Rationale: Minor clarifications to the text were made.	
Synopsis, Overview of Study Design	For consistency with the information in Section 9.1.2 (Screening/Prospective Observation Phase), text in the synopsis regarding the study criteria for nonresponse has been revised to now state "The site investigators will be blinded to the study criteria for nonresponse; therefore, this information is maintained in a separate document."
Time & Events Schedule	Added footnote "r" to Visit 2.1 C-SSRS (Since Last Visit) assessment to indicate this is only performed for subjects who do not have Visit 1.3 and 2.1 occur on the same day.
1. Introduction	The abbreviation TRD is now defined as "treatment-resistant depression". Text updated to indicate that the description of the mechanism of action of ketamine applies to esketamine as well.
1.1.2.2. Pharmacodynamics and Efficacy	The following text was added: "In Study ESKETINTRD2003, Panel A was conducted in the United States and Belgium and Panel B in Japan."
4. Study Population	Text revised to now state: "If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed."
6.1. Screening/Prospective Observational Phase	For consistency with other sections, a sentence was added to state that the sponsor will not supply antidepressant medication(s) during the screening/prospective observational phase.
9.2.1.1. Primary Efficacy Evaluation	The MADRS item previously described as "interest level" was changed to "inability to feel (interest level)".
9.3. Pharmacokinetics	The following text was added: "Whole blood samples will be used to evaluate the PK of esketamine. Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained".
9.6. Safety Evaluations	The statement in the section regarding vital signs now reads: "Blood pressure and pulse/heart rate measurements will be assessed in a supine position with a completely automated device or using manual techniques".

Applicable Section(s)	Description of Change(s)
12.3.2. Serious Adverse Events	With regard reporting serious adverse events, the following exception to reporting hospitalization of a subject has been modified to start: "For convenience the investigator may choose to hospitalize the subject during a treatment period".
16.2.2. Independent Ethics Committee or Institutional Review Board (IEC/IRB)	The phrase "where required" has been added to the following statement: "At least once a year, the IEC/IRB will be asked to review and reapprove this study".
17.4. Source Documentation	Text has been revised to reflect current requirements for source documents.
17.5. Case Report Form Completion	Text has been revised to reflect current requirements for completion of CRFs.
Throughout the protocol	Minor corrections have been made to the abbreviations and definitions of abbreviations. Minor edits have been made that do not change the meaning of the text.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-1 (08 June 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to allow for a 28 mg dose throughout the study, based on pharmacokinetic data from study ESKETINTRD1012 in elderly subjects.

Applicable Section(s)	Description of Change(s)
Rationale: Based on pharmacokinetic data from study ESKETINTRD1012 a change was made to allow a 28 mg dose of esketamine throughout the study which could potentially improve safety and tolerability	
1.1.2.1. Pharmacokinetics and Product Metabolism; 1.1.2.3. Safety and Tolerability	Description of preliminary pharmacokinetic results for study ESKETINTRD1012 was added in addition to a safety overview from the study.
1.1.2.2. Pharmacodynamics and Efficacy	Justification statement for including the 28 mg dose beyond Day 1 was added.
Synopsis Dosing and Administration; 3.1. Overview of Study Design; 3.2.4. Treatment Groups and Dose Selection	Change made to allow 28 mg dose of esketamine throughout the study, not just on Day 1. New table added to describe dose titration guidance.

Applicable Section(s)	Description of Change(s)
Synopsis; 1.2. Active Comparators in Double-blind Induction Phase; 1.3. Overall Rationale for the Study; 2.1. Objectives; 3.1. Overview of Study Design; 3.2.4. Treatment Groups and Dose Selection; 6.2. Double-Blind Induction Phase; 9.1.3. Double-Blind Induction Phase	Added 28 mg to the list of intranasal doses of esketamine used in this study. Removed references of 28 mg only being allowed on Day 1.
Rationale: More conservative blood pressure parameters related to patient dosing were incorporated to improve subject safety	
Synopsis Dosing and Administration; 6.2. Double-blind Induction Phase; 6.2.1. Guidance for Blood Pressure Monitoring on Dosing Days	Added that prior to intranasal dosing, subjects must have a pre-dose blood pressure \leq 150/90 mm Hg and prior to dose escalation, subjects must have had a post-dose blood pressure, on the prior intranasal dosing day, of $<$ 180 mm Hg for systolic and $<$ 100 mm Hg for diastolic blood pressure.
Rationale: Correction to Day 28 study window	
Time & Events Schedule	The study window for Day 28 of the induction phase was incorrectly listed as \pm 2 days. This window has been corrected to be -1 day.
Rationale: Collection of blood sample for Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations was moved to Study Day 28 so that it corresponds with the hematology sample collection	
Time & Events Schedule	Collection of blood sample for Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations was moved to Study Day 28 from the original Study Day 25.
Rationale: The frequency of assessments of the Sheehan Disability Scale was increased following feedback from the FDA	
Time & Events Schedule	An additional assessment for the SDS was added on Day 15 of the Induction Phase.
Rationale: Footnote for predose procedures to be followed in case dosing is delayed (within visit windows).	
Time & Events Schedule	A footnote 'o' was added to Study Drug - Intranasal esketamine or placebo.
Rationale: Footnote for rescheduling smell test assessments in case the subject has significant nasal congestion	
Time & Events Schedule;	A footnote 'p' was added to UPSIT and Smell Threshold Test.
9.6 UPSIT and Smell Threshold Test	A note for rescheduling UPSIT and Smell Threshold Test in case of nasal congestion was added.

Applicable Section(s)	Description of Change(s)
Rationale: Study drug accountability was added at two weeks after the last intranasal dose	
Time & Events Schedule	An assessment for study drug accountability was added at Visit 3.2 of the follow-up phase.
Rationale: Inclusion criteria modified to enroll subjects with a normal thyroid-stimulating hormone function or free thyroxine levels in case of subjects with no pre-existing history of hypothyroidism to ensure that the subject is medically stable	
4.1. Inclusion Criteria Direct-entry Subjects;	– Inclusion criterion for direct-entry subjects was modified to ensure a normal thyroid-stimulating hormone [TSH] function in case of subjects without a pre-existing history of hypothyroidism. If the TSH is below the normal range, free thyroxine (fT4) levels will be measured and if fT4 is within the normal range the subject can be enrolled.
Rationale: Inclusion criterion was expanded to include subjects using specific tricyclic antidepressants at a dose below the MGH-ATRQ minimum therapeutic dose.	
4.1. Inclusion Criteria Direct-entry Subjects	Inclusion criteria for direct-entry subjects was modified for accepting specific tricyclic antidepressants which are being taken at a dose below the MGH-ATRQ minimum therapeutic dose but achieve a blood level that is within the therapeutic range.
Rationale: Exclusion criteria expanded to include additional DSM-5 diagnostic codes for intellectual disability and autism spectrum disorder	
Synopsis Study Population; 4.2. Exclusion Criteria Direct-entry Subjects	Exclusion criterion for direct-entry subjects was expanded to include additional DSM-5 diagnostic codes for intellectual disability as well as autism spectrum disorder.
Rationale: Exclusion criteria modified to exclude all subjects who have previously received esketamine or ketamine regardless of the type of response based on PMDA feedback	
Synopsis Study Population; 4.2. Exclusion Criteria Direct-entry Subjects	Exclusion criterion was modified to exclude subjects who have previously received esketamine or ketamine.
Rationale: Clarification of dosing for subjects using an intranasal decongestant	
6.2 Double-blind Induction Phase	Text describing the guidance for use of an intranasal decongestant to reduce congestion before administering esketamine.
Rationale: Accounting for blood volume to match inclusion criteria	
9.1.1 Overview	Six mL blood accounting for determining tricyclic antidepressant blood levels of specific tricyclic antidepressants which are being taken at a dose below the MGH-ATRQ minimum therapeutic dose.
Rationale: Correction to match T&E Schedule	
9.1.1 Overview	Volume of blood to be collected from each user was modified to include 2.5 mL for biomarker RNA in the screening/prospective observational phase thereby increasing total volume collected to 125.5 mL.
Rationale: Correction to description of MMSE	
9.7. Other Evaluations	The description of the MMSE was incorrect. The statement “attention (total score, 5), calculation (total score, 5)” was changed to “attention and calculation (total score, 5)”.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of scoring of the PAQ assessments	
9.7. Other Evaluations	Text describing scoring of the PAQ was revised to indicate it is based on Question 1 (not 1c through 1f).
Rationale: Clarification that SIGMA is the structured interview guide of the MADRS	
9.2.1.1 Primary Efficacy Evaluation	The following sentence was added to describe the MADRS “The structured interview guide for the MADRS (SIGMA) will be used for each administration”.
Rationale: List of clinical laboratory tests revised to align with other protocols in the program	
9.6. Safety Evaluations	Total bilirubin was added to the serum chemistry panel.
Rationale: Correction to Site Independent Qualification Assessment	
9.7. Other Evaluations	Reference to telephone contact was removed from the description of the Site Independent Qualification Assessment.
Rationale: Update to include new template text for reporting abnormal pregnancy outcomes	
12.3.3. Pregnancy	Instructions for the reporting of abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) were added.
Rationale: Clarification of the supply of oral antidepressant that will be provided to subjects entering the follow-up phase	
Time & Events Schedule	Footnote “n” was added to the Induction Phase T&E stating that subjects entering the follow-up phase will be provided with a 2 week supply of oral antidepressant.
Synopsis Overview of Study Design and Dosage and Administration; 16.1. Study-specific Design Considerations; 6.2 Double-blind Induction Phase; 9.1.4 Follow-up Phase	Change the supply of oral antidepressant given during the follow-up phase from 4 weeks to 2 weeks.

SYNOPSIS

A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Intranasal Esketamine Plus an Oral Antidepressant in Elderly Subjects with Treatment-resistant Depression

Study Acronym: TRANSFORM-3

Major depressive disorder (MDD), a serious, recurrent, and disabling psychiatric illness, is the second leading cause of years lost to disability worldwide. MDD is associated with excess mortality and with years of potential life lost. About 30% of patients fail to achieve remission despite treatment with multiple antidepressant medications, and are considered to have treatment-resistant depression (TRD). There is a significant need to develop novel treatments based upon relevant pathophysiologic pathways underlying MDD for the rapid relief of symptoms of depression, especially in patients with TRD.

Depression in later life, traditionally defined as age older than 65 years, is associated with disability, increased mortality, and poorer outcomes from physical illness. In addition, the condition is often under-recognized and under-treated. In the PRISM-E study, a large study of older patients with MDD, 71% of the patients did not remit even after 6 months of standard of care treatment in specialty or integrated care treatment centers. Factors associated with non-remission included severity of depression at baseline, a family history of depression, comorbid anxiety, and general medical comorbidity. According to the World Health Organization (WHO) data, proportionately more people aged over 65 years commit suicide than any other age group, and most have major depression. Older people who attempt suicide, are more likely to die than younger people, while in those who survive, their prognosis is worse.

Ketamine and esketamine (S-ketamine, the S enantiomer of ketamine) are approved and widely used for the induction and maintenance of anesthesia via intramuscular (IM) or intravenous (IV) administration. The desired analgesic-anesthetic effects of ketamine and esketamine are attributed to the blockade of ionotropic *N*-methyl-D-aspartate (NMDA) glutamate receptors. The mechanism of action of ketamine and esketamine is distinct from conventional monoaminergic antidepressant treatments. Ketamine and esketamine profoundly affect fast excitatory glutamate transmission, increase brain-derived neurotrophic factor (BDNF) release, and stimulate synaptogenesis.

Janssen Research & Development (JRD) is developing intranasal esketamine as an antidepressant therapy. A higher NMDA receptor affinity of esketamine, as compared with ketamine, allows a lower volume of medication to be administered via the non-invasive and rapidly-absorbed intranasal route.

The current study is being conducted to evaluate the efficacy, safety, and tolerability of flexibly-dosed intranasal esketamine, plus a newly initiated oral antidepressant, in elderly subjects with TRD. The study will serve as a pivotal Phase 3 short-term efficacy and safety study in support of regulatory agency requirements for registration of intranasal esketamine for the treatment of TRD.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective of this study is to evaluate the efficacy of switching elderly subjects with TRD from a prior antidepressant treatment (to which they have not responded) to flexibly dosed intranasal esketamine (28 mg, 56 mg or 84 mg) plus a newly initiated oral antidepressant, compared with switching to a newly initiated oral antidepressant (active comparator) plus intranasal placebo, in improving depressive symptoms, as assessed by the change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from Day 1 (pre-randomization) to the end of the 4-week double-blind induction phase.

Secondary Objectives

- To assess the effect of intranasal esketamine plus a newly initiated oral antidepressant compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo on the following parameters in elderly subjects with TRD:
 - Depression response rates
 - Depression remission rates
 - Overall severity of depressive illness
 - Health-related quality of life and health status
- To investigate the safety and tolerability of intranasal esketamine plus a newly initiated oral antidepressant compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo in elderly subjects with TRD, including the following:
 - Treatment-emergent adverse events (TEAEs), including AEs of special interest
 - Local nasal tolerability
 - Effects on heart rate, blood pressure, respiratory rate, and blood oxygen saturation
 - Effects on alertness and sedation
 - Potential psychosis-like effects
 - Dissociative symptoms
 - Potential effects on cognitive function
 - Potential effects on suicidal ideation/behavior
 - Potential treatment-emergent symptoms of cystitis and/or lower urinary tract symptoms
 - Potential withdrawal and/or rebound symptoms following cessation of intranasal esketamine treatment
 - Potential effects on sense of smell
- To assess the pharmacokinetics (PK) of intranasal esketamine in elderly subjects with TRD receiving intranasal esketamine plus a newly- initiated oral antidepressant

Exploratory Objectives

- To assess the PK/pharmacodynamic (PK/PD) relationship of intranasal esketamine and MADRS total score in elderly subjects with TRD.
- To assess the potential relationship of biomarkers with response/nonresponse to intranasal esketamine or oral antidepressants in elderly subjects with TRD.

Hypothesis

The hypothesis for this study is that, in elderly subjects with TRD, switching from a failed antidepressant treatment to intranasal esketamine plus a newly initiated oral antidepressant is superior to switching to a newly initiated oral antidepressant treatment (active comparator) plus intranasal placebo in improving depressive symptoms.

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, active-controlled, multicenter study in male and female elderly subjects with TRD to assess the efficacy, safety, and tolerability of flexibly dosed intranasal esketamine (28 mg, 56 mg or 84 mg) plus a newly initiated oral antidepressant, compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo.

The study has 3 phases which are briefly described below.

Screening/prospective observational phase (4-week duration + optional 3-week taper period)

This phase will prospectively assess treatment response to the subject's current oral antidepressant treatment regimen.

At the start of the screening/prospective observational phase, the subject must have had documented nonresponse to at least one antidepressant treatment (based on MGH-ATRQ criteria) in the current episode of depression, and the subject is taking a different oral antidepressant treatment(s) (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other ongoing medications being taken for depression at screening (including adjunctive and augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4.

After 4 weeks, subjects who are nonresponders to their current oral antidepressant treatment may be eligible to proceed to the double-blind induction phase. Non-response at the end of the screening/prospective observational phase is defined as $\leq 25\%$ improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥ 24 on Week 2 and Week 4.

Eligible subjects who are entering the double-blind induction phase will discontinue all of their current medication(s) being used for antidepressant treatment, including adjunctive/augmentation therapies. Of note, subjects taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening/prospective observational phase can continue these medications, but no dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the screening/prospective observational phase. If clinically indicated, a subject's current antidepressant treatment(s) may be tapered and discontinued over an additional, optional period of up to 3 weeks per the local prescribing information or per clinical judgment. This 3 week period may also be used to optimize medical management if needed to facilitate subject participation (eg, treatment of blood pressure or diabetes, wean from other medications, etc.). In such cases, if there is no planned taper, the oral regimen should be continued in the interim and then discontinued by Day 1 of the double-blind induction phase.

As a new oral antidepressant will be initiated on Day 1 of the double-blind induction phase, eligible subjects who do not require a tapered discontinuation of their antidepressant treatment(s) can proceed immediately into the double-blind induction phase.

Double-blind induction phase (4-week duration)

Approximately 148 eligible subjects will be randomly assigned at a 1:1 ratio (n=74 per treatment arm) to receive double-blind intranasal treatment with either esketamine [28 mg, 56 mg or 84 mg], or placebo, starting with an initial dose of 28 mg on Day 1. The intranasal treatment sessions (esketamine or placebo) will occur twice weekly. In addition, all subjects will initiate a new, open-label oral antidepressant on Day 1 that will be taken daily for the duration of this phase. The assigned oral antidepressant will be 1 of 4 oral antidepressant medications (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]) that the subject has not previously had a nonresponse to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country.

Subjects taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening/prospective observational phase can continue these medications during the induction phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the induction phase, with the exception of the use of permitted benzodiazepine rescue medication.

After completing the double-blind induction phase, subjects may be eligible to participate in the subsequent Study ESKETINTRD3004 if they meet all other study entry criteria. Subjects who do not complete the double-blind induction phase of this study will not be eligible to participate in the ESKETINTRD3004 study. ESKETINTRD3004 is a long-term open-label safety study involving repeated open-label treatment sessions of intranasal esketamine.

If a subject withdraws from the study before the end of the double-blind induction phase for reasons other than withdrawal of consent, an Early Withdrawal visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase.

Follow-up phase (2-week duration)

This phase will include all subjects who withdraw early before the end of the double-blind induction phase, or choose not to participate, in the subsequent ESKETINTRD3004 safety study, and have received at least 1 dose of intranasal study medication in the double-blind induction phase. There will be no intranasal treatment sessions administered during this phase.

At the start of the follow-up phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the subject's treating physician. All subjects will be provided with an additional 2-week supply of the oral antidepressant medication to ensure that there is no interruption of oral antidepressant therapy during the transition to further clinical/standard of care. The decision to continue the oral antidepressant in this phase will be at the discretion of the investigator. However, in order to better assess potential withdrawal symptoms from intranasal study medication and facilitate maintenance of clinical benefit following cessation of intranasal dosing, the oral antidepressant medication should be continued for the 2 weeks of the follow-up phase unless determined as not clinically appropriate.

Taking into consideration the up to 3-week optional taper period, the maximum duration of an individual subject's study participation will be up to 13 weeks (for subjects completing the follow-up phase).

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study.

STUDY POPULATION

The study population will include elderly men and women, 65 years (inclusive) and older, who meet the Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-5) diagnostic criteria for single-episode MDD (if a single episode MDD, the duration of the episode must be ≥ 2 years) or recurrent MDD, without psychotic features, based upon clinical assessment, and confirmed by the Mini-International Neuropsychiatric Interview (MINI). In addition, the subject must have an Inventory of Depressive Symptomatology-Clinician rated, 30-item (IDS-C₃₀) total score of ≥ 31 , which corresponds to moderate to severe depression.

At the start of the screening/prospective observational phase, subjects must have had a nonresponse (ie, lack of clinically meaningful improvement, defined as $\leq 25\%$ improvement) to ≥ 1 but ≤ 8 (if current episode is > 2 years, upper limit is only applicable to the last 2 years) oral antidepressant treatments taken at an adequate dosage and for an adequate duration, as assessed using the Massachusetts General Hospital–Antidepressant Treatment Response Questionnaire (MGH-ATRQ) and documented by records (eg, medical/pharmacy/prescription records, a letter from the treating physician, etc.) for the current episode of depression.

In addition, the subject must currently be taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other medications being used for depression treatment (including adjunctive/augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase. Dose adjustments are permitted per clinical judgment, but

the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through to the end of Week 4.

Non-response at the end of the screening/prospective observational phase is defined as $\leq 25\%$ improvement in the MADRS total score and a MADRS total score of ≥ 24 on Week 2 and Week 4.

Treatment-resistant depression (TRD) is defined as a lack of clinically meaningful improvement after treatment with at least 2 different antidepressant agents prescribed in adequate dosages for adequate duration.

The subject's current major depressive episode, depression symptom severity (Week 1 MADRS total score ≥ 24 required), and antidepressant treatment response in the current depressive episode (retrospectively assessed) must be deemed valid for participation in the clinical study based on a Site Independent Qualification Assessment. The Site Independent Qualification Assessment is a tool to facilitate subject selection for MDD clinical studies, with a goal to ensure enrollment of subjects who have symptoms that reflect the current state of illness and that these symptoms can be reliably measured with appropriate measurement tools.

Potential subjects will be excluded from participating in the study if they have previously demonstrated nonresponse of depressive symptoms to esketamine or ketamine in the current major depressive episode, to all 4 of the oral antidepressant treatment options available for the double-blind induction phase (ie, duloxetine, escitalopram, sertraline, and venlafaxine XR) in the current major depressive episode (based on MGH-ATRQ), or to an adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/bilateral ECT. Subjects who received vagal nerve stimulation (VNS) or who received deep brain stimulation (DBS) in the current major depressive episode will be excluded. Subjects will also be excluded if they have a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features, bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current only), neurodegenerative disorder (eg, Alzheimer's Disease, Vascular dementia, Parkinson's disease with clinical evidence of cognitive impairment) or evidence of mild cognitive impairment (MCI), a Mini Mental State Examination (MMSE) score < 25 or < 22 for those subjects with less than an equivalent of high school education, intellectual disability (only DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder; if they have homicidal ideation/intent or suicidal ideation with some intent to act within 6 months prior to the start of the screening/prospective observational phase per the investigator's clinical judgment and/or based on the Columbia Suicide Severity Rating Scale (C-SSRS); or if they have a history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria.

DOSAGE AND ADMINISTRATION

Screening/prospective observational phase

At the start of the screening/prospective observational phase, the subjects must have had documented nonresponse to at least one antidepressant treatment (based on MGH-ATRQ criteria) in the current episode of depression, and the subject is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other medications being taken for depression at screening (including adjunctive/augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase for the prospective observation of a response or a nonresponse. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4.

The sponsor will not supply these antidepressant medications. Antidepressant treatment adherence during this phase will be assessed using the Patient Adherence Questionnaire (PAQ).

Subjects who are eligible to enter the double-blind induction phase: After the completion of 4 weeks of prospective antidepressant treatment and assessment of the antidepressant treatment response, all antidepressant treatment(s) will be discontinued, including adjunctive/augmentation therapies. If clinically indicated (eg, antidepressant treatments with short half-lives, such as paroxetine and venlafaxine XR, or tolerability concerns), the antidepressant treatment(s) may be tapered off and stopped over a period of up to 3 weeks per the local prescribing information or clinical judgment.

As a new oral antidepressant will be initiated on Day 1 of the double-blind induction phase, eligible subjects who do not require a tapered discontinuation of their antidepressant treatment(s) can proceed immediately into the double-blind induction phase.

Double-blind induction phase

During this phase, subjects will receive double-blind intranasal treatment with esketamine or placebo. In addition, subjects will simultaneously initiate a new, open-label oral antidepressant on Day 1 that will be continued for the duration of this phase.

Intranasal Study Medication

All subjects will self-administer the intranasal study drug (esketamine or placebo) at treatment sessions twice a week for 4 weeks at the study site. The first treatment session will be on Day 1. Intranasal treatment sessions should not take place on consecutive days.

- Prior to the first intranasal dose on Day 1, subjects will practice spraying (into the air, not intranasally) a demonstration intranasal device that is filled with placebo solution.
- Instructions for intranasal dosing:
 - After Day 1 (dose 28 mg), all dosing decisions are to be determined by the investigator based on efficacy and tolerability.
 - Prior to intranasal dosing, subjects must not have a blood pressure >150 mm Hg systolic and/or >90 mm Hg diastolic.
 - Prior to any dose escalation, subjects must have had a post-dose blood pressure, on the prior intranasal dosing day, of <180 mm Hg for systolic and <100 mm Hg for diastolic blood pressure.
- Dose titration of intranasal esketamine will be performed as outlined in the table below:

Dose Titration of Intranasal Esketamine*

Day	Dose	Dose Titration Guidance
Day 1	28 mg	
Day 4	28 or 56 mg	The dose may remain at 28mg or be increased to 56mg, as determined by the investigator based on efficacy and tolerability
Days 8, 11, 15	28, 56 or 84 mg	The dose may be maintained, increased or reduced by 28mg from the previous dosing session, as determined by the investigator based on efficacy and tolerability. No dose increase is permitted beyond Day 15.
Days 18, 22 and 25	28, 56 or 84 mg	No dose increase is permitted beyond Day 15. If needed for tolerability, dose reduction by 28mg from the previous dose is permitted on Days 18, 22 and 25.

* Dose changes are determined by the investigator based on efficacy and tolerability and in accordance with blood pressure guidelines.

From Day 8 to Day 15, inclusive, for those who have had a prior down titration from a higher dose, a dose increase by 28 mg is allowed based on clinical judgment.

On all intranasal treatment session days, a site staff member with training in cardiopulmonary resuscitation (eg, Basic Life Support course or equivalent courses) that is up to date per local regulations must be present with the subject during the intranasal treatment sessions and the postdose observation period. In addition, equipment for supportive ventilation and resuscitation needs to be present. Subjects must remain at the site until study procedures have been completed and the subject is ready for discharge. At the time of discharge, subjects should be accompanied by a responsible adult when released from the clinical site. Subjects must not drive a car or work with machines for 24 hours after receiving intranasal study drug.

Oral Antidepressant Study Medication

Starting on Day 1, a new, open-label oral antidepressant treatment will be initiated in all subjects. The oral antidepressant will be 1 of 4 oral antidepressant medications (duloxetine, escitalopram, sertraline, or venlafaxine XR). The antidepressant medication will be assigned by the investigator based on review of MGH-ATRQ and relevant prior antidepressant medication information, and will be one that the subject has not previously had a nonresponse to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country.

Dosing of the oral antidepressant will begin on Day 1. A mandatory titration schedule is provided in the protocol. Doses are not to exceed the maximum dose defined in the titration schedule. If higher doses are not tolerated, a down-titration is permitted based on clinical judgment.

All subjects will be provided with an additional 2-week supply of the oral antidepressant medication, to ensure that there is no interruption of oral antidepressant therapy during the transition to further clinical/standard of care in the follow-up phase.

Study-site personnel will instruct subjects on how to store and take the oral antidepressant treatment supplied during this study for at-home use. A subject diary will be provided to capture oral antidepressant study medication use.

On intranasal dosing days, it is recommended that the oral antidepressant medication not be taken until at least 3 hours after the intranasal treatment session.

Follow-up phase

At the start of the follow-up phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the subject's treating physician.

No intranasal study medication will be administered during this phase.

The decision to continue the oral antidepressant medication in this phase will be at the discretion of the investigator, however, in order to better assess potential withdrawal symptoms from intranasal study medication, the oral antidepressant medication should be continued for the follow-up phase unless determined as not clinically appropriate.

Subjects entering the follow-up phase will have 2 follow-up visits conducted at 1 and 2 weeks after the last dose of study medication. The follow-up visits at 1 and 2 weeks after the last dose of study medication will be a telephone contact and a clinical visit, respectively.

EFFICACY EVALUATIONS/ENDPOINTS

Primary Efficacy Evaluation and Endpoint

The primary efficacy/evaluation will be the MADRS total score. The MADRS will be performed by independent remote raters during the study. The MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment.

The primary efficacy endpoint will be the change from baseline in MADRS total score from Day 1 pre-randomization, to the end of the 4-week double-blind induction phase.

Secondary Efficacy Evaluations and Endpoints

Secondary efficacy evaluation endpoints include the change from baseline (Day 1 prior to randomization) to the end of the 4-week double-blind induction phase in:

- Proportion of responders ($\geq 50\%$ reduction from baseline in MADRS total score) at the end of the 4-week double-blind induction phase
- Proportion of subjects in remission (MADRS ≤ 12) at the end of the 4-week double-blind induction phase
- Change from baseline (Day 1 prior to randomization) to the end of the 4-week double-blind induction phase in:
 - Severity of depressive illness, using the Clinical Global Impression – Severity (CGI-S)
 - Health-related quality of life and health status, as assessed by the EuroQol-5 dimension-5 level (EQ-5D-5L).

PHARMACOKINETIC EVALUATIONS

Plasma samples will be analyzed to determine concentrations of esketamine (and noresketamine, if warranted) using a validated, specific, achiral, and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method by or under the supervision of the sponsor. Plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method. In addition, plasma PK samples may be stored for future analysis of the metabolite profile.

BIOMARKER, PHARMACOGENOMIC (DNA), AND EXPRESSION (RNA) EVALUATIONS

Assessment of biomarkers (protein and RNA) and their potential relationship to intranasal esketamine plus a newly initiated oral antidepressant and to maintenance/stabilization of response, nonresponse, and relapse will be explored. Blood samples will be collected to measure genetic and epigenetic markers (including but not limited to BDNF allelic variants) and protein markers (including but not limited to growth factors, inflammation, endocrine, or metabolic markers). Samples of deoxyribonucleic acid (DNA) and biomarkers (protein and RNA) may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

SAFETY EVALUATIONS

Safety evaluations will include:

- Monitoring of TEAEs, including TEAEs of special interest, clinical laboratory tests (including hematology, serum chemistry, and urinalysis), urine drug screen, 12-lead electrocardiogram, vital signs, pulse oximetry, physical examination, and body weight measurements
- Nasal examinations and nasal symptom questionnaire
- Columbia Suicide Severity Rating Scale (C-SSRS), to assess potential suicidal ideation and behavior

- Clinician Administered Dissociative States Scale (CADSS), to assess the treatment-emergent dissociative symptoms
- Four-item positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS+), to assess potential treatment-emergent psychotic symptoms
- Modified Observer's Assessment of Alertness/Sedation (MOAA/S), to measure treatment-emergent sedation
- Clinical Global Assessment of Discharge Readiness (CGADR), to document the subject's current clinical status and is the clinician's assessment of the readiness to be discharged from the study site
- Physician Withdrawal Checklist (20 items; PWC-20) to assess potential withdrawal symptoms following cessation of intranasal esketamine treatment
- Bladder Pain/ Interstitial Cystitis Symptom Score (BPIC-SS), to monitor subjects for potential symptoms of cystitis, bladder pain, and interstitial cystitis
- Computerized cognitive battery and Hopkins Verbal Learning Test-Revised (HVLTR), to assess the effect of intranasal esketamine on cognition
- University of Pennsylvania Smell Identification Test (UPSIT), to assess any potential treatment-emergent effects on the sense of smell.

STATISTICAL METHODS

Subject Information

The primary efficacy and safety analysis sets are defined below.

- **Full Analysis Set:** All randomized subjects who receive at least 1 dose of intranasal study medication and 1 dose of oral antidepressant medication in the double-blind induction phase.
- **Safety Analysis Set:** All randomized subjects who receive at least 1 dose of intranasal study medication or 1 dose of oral antidepressant medication in the double-blind induction phase.

Sample Size Determination

The maximum sample size planned for this study was calculated assuming a treatment difference at the end of the double-blind induction phase of 6.5 points in MADRS total score between esketamine and the active comparator, a standard deviation of 12, a 1-sided significance level of 0.025, and a drop-out rate of 25%. A maximum of about 74 subjects will need to be randomized to each treatment group to achieve 80% power using a fixed design with no interim analysis. The treatment difference and standard deviation used in this calculation were based on results of Panel A from the ESKETINTRD2003 study and on clinical judgment.

Interim Analysis for Sample Size Re-Estimation or Stopping for Futility

One unblinded interim analysis will be performed 4 weeks after randomizing 50 subjects in the study (approximately 25 per treatment group). It is projected that at that time approximately 36 subjects in the full analysis set would have completed the double-blind induction phase of the study (approximately 18 subjects per treatment group). The dropout rate will be monitored to ensure a sufficient number of subjects are included in the interim analysis. As the assumptions of the expected treatment difference and variability may or may not be upheld, the purpose of the interim analysis is to either re-estimate sample size or to stop the study due to futility. The sample size may be adjusted to achieve the desired power while maintaining control of the overall Type I error. The maximum sample size planned for this study is 74 per treatment group. The study team will be blinded to the results of the interim analysis and any adjustments that will be made to the sample size. However, the clinical supplies group will be informed

of the decision made at the interim analysis so that only the required amount of study medication will be packaged.

Primary and Secondary Efficacy Analyses

With the exception of the European Union (EU) dossier, the primary efficacy variable, change from baseline in MADRS total score at Week 4 in the double-blind induction phase, will be analyzed using a mixed-effects model for repeated measures (MMRM). The model will include baseline MADRS total score as a covariate, and treatment, country, class of antidepressant (Serotonin and Norepinephrine Reuptake Inhibitors [SNRI] or Selective Serotonin Reuptake Inhibitors [SSRI]), day, and day-by-treatment interaction as fixed effects, and a random subject effect. Comparison of the intranasal esketamine plus oral antidepressant arm versus oral antidepressant plus intranasal placebo will be performed using the appropriate contrast.

For the EU dossier, the primary efficacy analysis will be based on an analysis of covariance (ANCOVA) model using last observation carried forward (LOCF) data. The model will include factors for treatment, country, and class of oral antidepressant (SNRI or SSRI) and baseline MADRS total score as a covariate. Comparison of the intranasal esketamine plus oral antidepressant arm versus intranasal placebo plus oral antidepressant will be performed using the appropriate contrast.

Response and remission rates will be summarized at each visit

The ranks of change from baseline in CGI-S scores at the end of the double-blind induction phase will be analyzed based on LOCF data using an ANCOVA model, with country and class of antidepressant (SNRI or SSRI) as factors, and the baseline score (unranked) as the covariate.

Dimension scores of the EQ-5D-5L, descriptive system, the health status index, and the EQ visual analog scale (EQ-VAS) scores will be summarized over time.

Additionally, scores of all efficacy endpoints will be summarized for all visits in the double-blind induction phase. Summaries will be provided to show consistency of effect among relevant subgroups (eg, antidepressant class SNRI and SSRI).

PK Analyses

Plasma esketamine (and noresketamine, if warranted) concentrations will be listed for all subjects. The plasma concentration-time data of esketamine (and noresketamine, if warranted) will be analyzed using population PK modeling. Data may be combined with those of other selected studies to support a relevant structural model. Typical population values of basic PK parameters will be estimated together with the inter-individual variability. Effects of subject demographics, laboratory parameter values, and other covariates on the PK of esketamine will be explored. The results of the population PK analyses may be reported separately.

PK/PD Analyses

The relationship between the MADRS total score (and possibly selected adverse events as additional PD parameters), and PK metrics of esketamine, may be evaluated. If there is any visual trend in graphical analysis, suitable models will be applied to describe the exposure-effect relationships. The results of the PK/PD analyses may be reported separately.

Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Analyses

Baseline biomarker values and changes from baseline biomarker values to the time points specified in the Time and Events Schedule will be summarized. Exploratory biomarker analyses may include

comparisons of biomarker measures between the treatment groups, correlation with efficacy and other measures, and relationships with clinical response, relapse, and nonresponse.

The analysis plan and summarized results from both biomarker and pharmacogenomics analyses will be reported separately.

Safety Analyses

All safety data will be analyzed separately for the double-blind induction phase and the follow-up phase.

The verbatim terms used in the electronic case report form (eCRF) by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the double-blind induction phase (ie, TEAEs, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. Adverse events occurring during the follow-up phase will be summarized separately.

TEAEs of special interest will be examined separately grouped in the following categories: Drug abuse, dependence and withdrawal (standardized MedDRA queries [SMQ]), increased blood pressure, increased heart rate, transient dizziness/vertigo, impaired cognition, anxiety, and cystitis. Adverse events of special interest will be further listed in the SAP.

Subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event will be summarized separately.

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point in each phase of the study. Changes from baseline results will be presented. Frequency tabulations of the abnormalities will be provided. Listings of subjects with laboratory results outside the reference ranges and markedly abnormal results will also be provided.

Electrocardiogram (ECG) data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made. The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: QT corrected according to Fridericia's formula (QTcF), which will be the primary correction factor, and QT corrected according to Bazett's formula (QTcB).

Descriptive statistics of QTc intervals and changes from double-blind baseline will be summarized at each scheduled time point. The percentage of subjects with QTc interval >450 msec, >480 msec, or >500 msec will be summarized, as will the percentage of subjects with QTc interval increases from baseline <30 msec, 30-60 msec, or >60 msec.

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, pulse oximetry, and blood pressure (systolic and diastolic) (supine) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

Changes in findings from the baseline nasal examination (including the upper respiratory tract/throat) will be listed by treatment group. Examinations will provide ratings (absent, mild, moderate, or severe) that are based on a visual inspection of the nostrils, nasal mucosa, and throat for nasal erythema, rhinorrhea, rhinitis, capillary/blood vessel disruption and epistaxis. A shift table for changes from double-blind baseline in ratings for each examination will be presented by treatment group.

Scoring from the nasal symptom questionnaire will be summarized descriptively for each scheduled time point by treatment group.

Suicide-related thoughts and behaviors based on the C-SSRS will be summarized by treatment group in incidence and shift tables. Separate endpoints for suicidal ideation and suicidal behavior will be defined and summarized descriptively by treatment group.

Descriptive statistics of the CADSS, BPRS+, and MOAA/S scores and changes from predose will be summarized at each scheduled time point.

Descriptive statistics of the CGADR, PWC-20, BPIC-SS, UPSIT scores and changes and/or percent changes from baseline will be summarized at each scheduled time point.

Descriptive statistics of each cognitive domain score and changes from baseline will be summarized at each scheduled time point.

TIME AND EVENTS SCHEDULE (Screening/Prospective Observational Phase and Double-blind Induction Phase)

Phase	Screening/ Prospective Observational Phase			Double-blind Induction Phase									
	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	EW ^b
Visit number													
Week	Week 1	End of Week 2	End of Week 4	1	2	3	4						
Study day	-	-	-	1 (baseline)	4	8	11	15	18	22	25	28	EW
Clinical visit window (in days)	-	±2	±2	-	±1	±1	±1	±1	±1	±1	±1	±1	-
Clinical visit (C)	C	C	C	C	C	C	C	C	C	C	C	C	C
Screening/Administrative													
Informed consent (ICF)	X												
Medical history, psychiatric history, demographics, and employment status	X												
MINI	X												
MMSE	X												
MGH-ATRQ	X												
Site Independent Qualification Assessment	X												
Height	X												
Inclusion/exclusion criteria	X			X									
Prestudy therapy	X												
Preplanned surgery/procedures	X												
STOP Bang questionnaire (including assessment of BMI and neck circumference)	X												
IDS-C ₃₀	X												
Study Drug													
Randomization				X									
Dispensing of new oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR)				X								X ⁿ	X
Practice session for use of intranasal device ^d				X									
Intranasal esketamine or placebo ^o				X	X	X	X	X	X	X	X		
Drug accountability (intranasal study medication)				X	X	X	X	X	X	X	X		X

Phase	Screening/ Prospective Observational Phase			Double-blind Induction Phase									
	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	EW ^b
Visit number	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	EW ^b
Week	Week 1	End of Week 2	End of Week 4	1	2	3	4						
Study day	-	-	-	1 (baseline)	4	8	11	15	18	22	25	28	EW
Clinical visit window (in days)	-	±2	±2	-	±1	±1	±1	±1	±1	±1	±1	±1	-
Clinical visit (C)	C	C	C	C	C	C	C	C	C	C	C	C	C
Drug accountability (oral antidepressant study medication)				X								X	X
Dispense subject diary for oral antidepressant				X									
Review subject diary and update (if applicable)					X	X	X	X	X	X	X	X	X
Oral antidepressant compliance check						X		X		X		X	X
Return of subject diary if not entering follow up phase												X	
Safety Assessments (Clinician)													
Physical examination	X			X								X	X
Nasal examination ^d	X			X								X	X
Vital signs: blood pressure, pulse, respiratory rate, temperature ^{d,o}	X			X	X	X	X	X	X	X	X		X
Vital signs (postdose): blood pressure, pulse, respiratory rate ^{e,o}				X	X	X	X	X	X	X	X		
Weight	X			X								X	X
12-lead ECG ^{f,o}	X			X	X	X	X	X	X	X	X		X
C-SSRS: Baseline/Screening version	X												
C-SSRS: Since last visit version ^{d,o}		X	X	X ^r	X	X	X	X	X	X	X	X	X
MOAA/S ^{g,o}				X	X	X	X	X	X	X	X		
Pulse oximetry ^{g,o}	X			X	X	X	X	X	X	X	X		
BPRS ^{+h,o}				X	X	X	X	X	X	X	X		
CADSS ^{h,o}				X	X	X	X	X	X	X	X		
CGADR ⁱ				X	X	X	X	X	X	X	X		
PWC-20											X ^j		X
Safety Assessments (Subject-completed)													
Nasal symptom questionnaire ^k				X	X		X		X		X		
BPIC-SS ^d				X				X				X	X

Phase	Screening/ Prospective Observational Phase			Double-blind Induction Phase									
	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	EW ^b
Visit number													
Week	Week 1	End of Week 2	End of Week 4	1	2	3	4						
Study day	-	-	-	1 (baseline)	4	8	11	15	18	22	25	28	EW
Clinical visit window (in days)	-	±2	±2	-	±1	±1	±1	±1	±1	±1	±1	±1	-
Clinical visit (C)	C	C	C	C	C	C	C	C	C	C	C	C	C
Assessment of Sense of Smell													
UPSIT ^{d,p}		X										X	X
Efficacy Assessments (Clinician)													
MADRS (performed by independent, remote raters)	X	X ^q	X ^q	X ^{c,q}		X ^{d,q}		X ^{d,q}		X ^{d,q}		X ^q	X
CGI-S ^d	X			X	X	X	X	X	X	X	X	X	X
Efficacy Assessments (Subject-completed)													
PAQ	X	X	X										
EQ-5D-5L ^d	X			X				X				X	X
Cognition Testing^s													
Practice sessions for computerized test battery		X											
Computerized test battery and HVLTR				X ^d								X	X
Clinical Laboratory Assessments													
TSH, HbA1c	X												
Lipid panel (fasting)		X											
Hematology, chemistry ^d	X			X								X	X
Urine drug screen ^d	X			X				X			X		
Alcohol breath test	X			X									
Urinalysis ^d	X			X				X				X	X
Pharmacokinetics													
Blood collection ^l										X			
Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations													
Blood sample collection (protein) ^{m,d}	X			X	X	X						X	X
Blood sample collection (DNA) ^{m,d}	X											X	X
Blood sample collection (RNA) ^{m,d}	X			X	X	X						X	X

Phase	Screening/ Prospective Observational Phase			Double-blind Induction Phase									
	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	EW ^b
Visit number	1.1	1.2	1.3 ^a	2.1 ^a	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	EW ^b
Week	Week 1	End of Week 2	End of Week 4	1	2	3	4						
Study day	-	-	-	1 (baseline)	4	8	11	15	18	22	25	28	EW
Clinical visit window (in days)	-	±2	±2	-	±1	±1	±1	±1	±1	±1	±1	±1	-
Clinical visit (C)	C	C	C	C	C	C	C	C	C	C	C	C	C
Ongoing Subject Review													
Concomitant Therapy	Ongoing												
Adverse Events	Ongoing												

Footnotes:

Abbreviations: BMI=body mass index; BPIC-SS=Bladder Pain/Interstitial Cystitis Symptom Score; BPRS+=Four-item positive symptom subscale of the Brief Psychiatric Rating Scale; CADSS=Clinician Administered Dissociative States Scale; CGADR=Clinical Global Assessment of Discharge Readiness; CGI-S=Clinical Global Impression – Severity; C-SSRS=Columbia Suicide Severity Rating Scale; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EQ-5D-5L=EuroQol-5 dimension, 5-level; EW=early withdrawal; HbA1C=glycosylated hemoglobin; HVLT-R=Hopkins Verbal Learning Test-Revised; IDS-C₃₀=Inventory of Depressive Symptomatology Clinician-rated 30-item scale; MADRS=Montgomery-Asberg Depression Rating Scale; MGH-ATRQ=Massachusetts General Hospital Antidepressant Treatment History Questionnaire; MINI=Mini International Neuropsychiatric Interview; MMSE=Mini Mental State Examination; MOAAS=Modified Observer's Assessment of Alertness/Sedation; PAQ=Patient Adherence Questionnaire; PWC-20=20-item Physician Withdrawal Checklist; RNA=ribonucleic acid; STOP-Bang=Snoring, Tired, Observed Apnea, High Blood Pressure, Body mass index, Age, Neck Size, Gender (a questionnaire); TSH=thyroid-stimulating hormone; UPSIT= University of Pennsylvania Smell Identification Test

Note: On intranasal dosing days, time 0 is defined as the time of the first intranasal spray. Therefore postdose time points are referenced from this.

- An additional, optional period of up to 3 weeks is permitted to taper and discontinue current antidepressant treatment(s) after completion of the Week 4 (Visit 1.3) assessments, per the local prescribing information or clinical judgment. This 3 week period may also be used to optimize medical management if needed to facilitate subject participation. Subjects who do not require a taper and are thus eligible to immediately proceed to the double-blind induction phase can have Visits 1.3 and 2.1 occur on the same day or within 1 week of each other (if not occurring on the same day, the antidepressant treatment regimen should be continued after visit 1.3. and then discontinued prior to Visit 2.1).
- If a subject withdraws before the end of the double-blind induction phase (ie, before completing Visit 2.9/Day 28) for reasons other than withdrawal of consent, and an early withdrawal visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase. If the early withdrawal visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.
- Performed for subjects requiring a taper period during the screening/prospective observational phase; the result will be the subject's baseline MADRS for the double-blind induction phase. For all other subjects, the baseline MADRS for the double-blind induction phase will be the MADRS performed at the end of Week 4 of the screening/prospective observational phase.

- d) Predose (if/when performed on intranasal dosing days). Predose subject-reported outcome assessments should be administered before all other study-related procedures during a clinic visit.
- e) Postdose vital signs will be measured at 40 minutes, 1 hour, and 1.5 hours postdose. Please refer to Section 6.2.1 for guidance on blood pressure monitoring on dosing days.
- f) Twelve-lead ECG will be performed predose and at t=1 hour postdose at Visit 2.1. Twelve-lead ECG will be performed at t=1 hour postdose (no predose) at Visits 2.2 through 2.8. A time window of ± 15 minutes is permitted.
- g) The MOAA/S will not be performed at Visit 1 (pulse oximetry only). The MOAA/S will be performed every 15 minutes from predose to t=+1.5 hours postdose (please refer to Section 9.6 for further guidance on MOAA/S assessments). Pulse oximetry will be performed every 15 minutes from predose to t=1.5 hours postdose (please refer to Section 9.6 for further guidance regarding on timing of pulse oximetry assessments).
- h) The BPRS+ and CADSS to be performed predose and at 40 minutes and 1.5 hours postdose.
- i) CGADR to be performed at 1 hour and 1.5 hours postdose; if the response is not “Yes” at 1.5 hours postdose, the assessment will be repeated every 15 minutes until a “Yes” response is achieved or until the subject is referred for appropriate medical care if clinically indicated. A subject should not be discharged prior to the 1.5 hour time point.
- j) PWC-20 to be performed predose on all subjects.
- k) Nasal symptom questionnaire will be performed predose and at 1 hour postdose.
- l) PK blood collection will be performed at t=40 minutes and t=2 hours postdose (where time=0 is defined as the time of the first intranasal spray).
- m) Blood samples should be collected prior to dosing. It is preferred that subjects adhere to a low fat diet on the day of sample collection.
- n) Only subjects entering the follow-up phase will be provided with a 2-week supply of oral antidepressant.
- o) If intranasal dosing is postponed (but occurs within visit window) due to vital sign results (eg, blood pressure elevation), all assessment time points (including predose) must be performed on the actual intranasal dosing day.
- p) If on the day of the scheduled smell test assessments the subject has significant nasal congestion, the site should consider postponing to the next scheduled visit.
- q) The MADRS should be administered no more than 2 days prior to the subject’s targeted (not actual) clinic visit date (except Visit 2.9, which is within 1 day prior). If performed on the day of the scheduled clinic visit for an intranasal treatment session, the MADRS must be performed prior to the intranasal treatment session.
- r) Performed only if Visit 1.3 and Visit 2.1 do not occur on the same day.
- s) Testing can precede Visit 2.1.

TIME AND EVENTS SCHEDULE (Follow-up Phase)

Visit Number	Follow-up Phase	
	3.1	3.2
Weeks after last intranasal dose	1	2
Visit window for clinic visit or remote assessments only (days)	±3	±3
Clinical visit (C) or remote assessments only (RA)	RA ^c	C
Oral antidepressant compliance^a		
Oral antidepressant compliance check		X
Return of subject diary		X
Safety assessments (Clinician-completed)		
Physical examination		X
Nasal examination		X
Vital signs: Blood pressure, pulse, respiratory rate, temperature		X
12-lead ECG		X
C-SSRS: Since last visit version		X
PWC-20	X ^b	X
Safety assessments (Subject-completed)		
BPIC-SS		X
Efficacy assessments (Clinician-completed)		
MADRS (performed by independent, remote raters) ^c	X	X
CGI-S		X
Efficacy assessments (Subject-completed)		
EQ-5D-5L		X
Cognition testing		
Computerized test battery and HVLIT-R		X
Clinical laboratory assessments		
Hematology, chemistry		X
Urinalysis		X
Biomarker and Expression (RNA) evaluations		
Blood sample collection (protein) ^d		X
Blood sample collection (RNA) ^d		X
Study Drug		
Drug Accountability		X

Visit Number	Follow-up Phase	
	3.1	3.2
Weeks after last intranasal dose	1	2
Visit window for clinic visit or remote assessments only (days)	±3	±3
Clinical visit (C) or remote assessments only (RA)	RA ^c	C
Ongoing subject review		
Concomitant therapy	Ongoing	
Adverse events	Ongoing	

Footnotes:

Abbreviations: BPIC-SS=Bladder Pain/Interstitial Cystitis Symptom Score; CGI-S=Clinical Global Impression – Severity; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; EQ-5D-5L=EuroQol-5D, 5-level; HVLT-R=Hopkins Verbal Learning Test-Revised; PWC-20=20-item Physician Withdrawal Checklist; RNA=ribonucleic acid.

Note: No intranasal study medication will be administered during this phase.

- In order to better assess potential withdrawal symptoms from intranasal study medication, the oral antidepressant medication should be continued for the 2 weeks of the follow-up phase, unless determined to be not clinically appropriate.
- Performed by telephone by qualified site staff.
- MADRS will be performed by an independent remote rater. At Visit 3.1 (Week-1 of follow-up) the subject will have the MADRS assessment with a remote rater visit, in addition to a follow-up call from the site.
- It is preferred that subjects adhere to a low fat diet on the day of sample collection.
- For the Remote Assessment (RA) Visit 3.1, site staff will contact the subject by telephone to obtain information regarding adverse events and concomitant therapies.

ABBREVIATIONS

AHI	apnea-hypopnea index
ANCOVA	analysis of covariance
ASA	American Society of Anesthesiologists
AUC	area under the plasma concentration-time curve
BDNF	brain-derived neurotrophic factor
BMI	body mass index
BPIC-SS	Bladder Pain/ Interstitial Cystitis Symptom Score
BPRS+	four-item positive symptom subscale of the Brief Psychiatric Rating Scale
CADSS	Clinician Administered Dissociative States Scale
CGADR	Clinical Global Assessment of Discharge Readiness
CGI-S	Clinical Global Impression – Severity
C	clinic visit
C _{max}	maximum plasma concentration
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450, with appended letters (eg, 2B6, 3A4) indicating subtype
DBP	diastolic blood pressure
DBS	deep brain stimulation
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th Edition)
ECG	electrocardiogram
eCRF	electronic case report form
ECT	electroconvulsive therapy
eDC	Electronic Data Capture
EQ-5D-5L	EuroQol; 5 dimension; 5 level
EQ-VAS	EuroQol group: Visual Analogue Scale
EU	European Union
EW	Early Withdrawal
FAS	full analysis set
FDA	Food and Drug Administration
ft4	free thyroxine
GCP	Good Clinical Practice
HbA1c	glycated hemoglobin
HDRS	Hamilton Depression Rating Scale
HIV	human immunodeficiency virus
HPA	hypothalamic pituitary adrenal
HVLT-R	Hopkins Verbal Learning Test-Revised
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDS-C ₃₀	Inventory of Depressive Symptomatology-Clinician rated, 30-item scale
IEC	Independent Ethics Committee
IM	intramuscular
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LOCF	last observation carried forward
MADRS	Montgomery Asberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire
MINI	Mini International Neuropsychiatric Interview (mental status questionnaire)
MOAA/S	Modified Observer’s Assessment of Alertness/Sedation
MMRM	mixed-effects model for repeated measures
NMDA	<i>N</i> -Methyl-D-Aspartate

PAQ	Patient Adherence Questionnaire
PCP	phencyclidine
PD	pharmacodynamics
PK	pharmacokinetics
PQC	product quality complaint
PRISM-E	Primary Care Research in Substance Abuse and Mental Health for the Elderly
PWC-20	Physician Withdrawal Checklist; 20-item
QIDS-SR ₁₆	Quick Inventory of Depressive Symptomatology – Self Report
QTc	QT interval corrected
QTcB	QT interval corrected according to Bazett's formula
QTcF	QT interval corrected according to Fridericia's formula
RA	remote assessments only
RNA	ribonucleic acid
SAP	statistical analysis plan
SBP	systolic blood pressure
SmPC	Summary of Product Characteristics
SMQ	standard Medical Dictionary for Regulatory Activities query
SNRI	Serotonin and Norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
STOP-Bang	snoring, tired, observed apnea, high blood pressure, body mass index, age, neck size, gender (questionnaire)
SUSAR	suspected unexpected serious adverse reaction
T _{max}	time to reach the maximum plasma concentration
TEAE	treatment-emergent adverse event
TRD	treatment-resistant depression
TSH	thyroid-stimulating hormone
UPSIT	University of Pennsylvania Smell Identification Test
US	United States
US FDA	United States Food and Drug Administration
VNS	vagal nerve stimulation
XR	extended release

1. INTRODUCTION

Major depressive disorder (MDD) is a serious, recurrent, and disabling psychiatric illness.⁹⁰ It is the second leading cause of years lost to disability worldwide and is associated with excess mortality, and the estimated median years of potential life lost is 10 years.^{91,95} About 30% of patients fail to achieve remission despite treatment with multiple antidepressant medications, and are considered to have treatment-resistant depression (TRD).^{32,77} In patients who respond to antidepressant treatments, the time to onset of effect is typically 4 to 7 weeks, during which time patients continue to suffer from their symptoms and continue to be at risk of self-harm, as well as being impacted by the associated harm to their personal and professional lives.^{77,80} Therefore, there is a significant need to develop novel treatments based upon relevant pathophysiologic pathways underlying MDD for the rapid relief of depressive symptoms, especially in patients with TRD.^{19,25}

Depression in later life, traditionally defined as age older than 65 years, is associated with disability, increased mortality, and poorer outcomes from physical illness and in addition, the condition is often under-recognized and under-treated.⁷³ In the Primary Care Research in Substance Abuse and Mental Health for the Elderly (PRISM-E) study, a large study of older patients with major depressive disorder, 71% of the patients did not remit even after 6 months of standard of care treatment in specialty or integrated care treatment centers.² Factors associated with non-remission included severity of depression at baseline, a family history of depression, comorbid anxiety, and general medical comorbidity. According to the World Health Organization (WHO) data, proportionately more people aged over 65 years commit suicide than any other age group; most have major depression. Older people who attempt suicide, are more likely to die than younger people, while in those who survive, prognosis is worse for older adults.⁴⁹

Ketamine and esketamine (S-ketamine, the S enantiomer of ketamine) are approved and widely used for the induction and maintenance of anesthesia via intramuscular (IM) or intravenous (IV) administration.⁴⁵ The desired analgesic-anesthetic effects of ketamine and esketamine are attributed to the blockade of ionotropic *N*-methyl-D-aspartate (NMDA) glutamate receptors.^{52,66,98}

Monoamines (serotonin, norepinephrine, and/or dopamine) are only modulatory transmitters; therefore, conventional monoaminergic antidepressant treatments would not be expected to robustly affect synaptic transmission, activity-dependent release of brain-derived neurotrophic factor (BDNF), or synaptogenesis.²⁵ In contrast, the mechanism of action of ketamine and esketamine is distinct from conventional antidepressant treatments because both ketamine and esketamine profoundly affect fast excitatory glutamate transmission, increase BDNF release, and stimulate synaptogenesis.²⁵

Most literature reports of the antidepressant effects of ketamine describe studies using IV administration of the racemate.^{16,60} Janssen Research & Development (JRD) is developing intranasal esketamine as an antidepressant therapy because it has higher NMDA receptor affinity which allows a lower volume of medication to be administered via the intranasal route.^{51,62,67}

For the most comprehensive nonclinical and clinical information regarding esketamine (JNJ-54135419), please refer to the latest edition of the Investigator's Brochure.⁴²

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

1.1.1. Summary of Nonclinical Findings

Safety Pharmacology

The following text is quoted from the US prescribing information for anesthetic Ketalar[®] (ketamine hydrochloride [HCl] injection).⁴⁵ Intravenous Ketalar produces a fall in arterial blood pressure in the Rhesus monkey and a rise in arterial blood pressure in the dog. In this respect the dog mimics the cardiovascular effect observed in man. The pressor response to Ketalar injected into intact, unanesthetized dogs is accompanied by a tachycardia, rise in cardiac output and a fall in total peripheral resistance. The pressor response to Ketalar is reduced or blocked by chlorpromazine (central depressant and peripheral α -adrenergic blockade), by β -adrenergic blockade, and by ganglionic blockade.

Findings from animal studies suggest that the increase in blood pressure produced by ketamine/esketamine is due to selective activation of central cardiac stimulating mechanisms leading to an increase in cardiac output.

In a 3-month repeat-dose toxicity study with intranasally administered esketamine in dogs, no relevant electrocardiogram (ECG) changes were noted up to the highest dose tested, ie, 72 mg/day. Heart rate was slightly increased. The cardiovascular safety of racemic ketamine and esketamine in humans and animals is summarized in the Investigator's Brochure.⁴²

Toxicology

Repeat-Dose Toxicity Studies

In repeat-dose toxicity studies with intranasally administered esketamine in rats up to 9 mg/day for 6 months, and dogs up to 72 mg/day for 3 months of duration, the clinical observations mainly related to the central nervous system (eg, changes in activity and gait). No adverse effects were noted up to the highest dose tested, ie, 9 mg/day in rats and 72 mg/day in dogs. These observations reflected the (exaggerated) pharmacology of the test compound. Minor histologic findings were noted in the nasal cavity. These tissue changes were not considered adverse.

In 3- and 9-month repeat-dose toxicity studies with intranasally administered esketamine in dogs, no relevant electrocardiogram (ECG) changes were noted up to 72 mg/day. Heart rate was slightly increased.

Further details can be found in the Investigator's Brochure.⁴²

Genetic Toxicity

A series of in vitro and in vivo genotoxicity studies were conducted with ketamine and esketamine. The weight of evidence indicates that esketamine poses no genotoxic risk to humans.⁴²

Neurotoxicity

Racemic ketamine has been reported to induce neurotoxicity in animal fetuses, and in juvenile, adolescent, and adult animals, as evidenced by histopathologic brain lesions and functional sequelae. The precise thresholds for dose and duration of exposure causing neurotoxicity in animals remain to be established. The relevance to humans of ketamine's neurotoxic action in animals is unknown.

In studies exploring neurotoxic effects of ketamine on juvenile and prenatal monkeys, neuroapoptosis was observed to be more widespread in fetal brains than in neonatal brains, after administration of ketamine anesthesia IV for 5 hours. In fetal brains, the cerebellum, caudate nucleus, putamen, and nucleus accumbens were most severely affected. In neonatal brains, the cerebellum was not affected; the strongest neuroapoptotic response was noted in the basal ganglia and several thalamic areas.

In juvenile rodents, ketamine induced apoptotic neurodegeneration was observed, that was more widespread than in adult rodents, with the developing brain affected in several major regions. Neuronal cell death was induced in the dorsolateral thalamus at blood levels of ketamine of 14 µg/mL (7 times the human anesthetic blood level of approximately 2 µg/mL).

No significant neurotoxic effects occurred in juvenile Rhesus monkeys if the anesthesia was administered as IM induction followed by IV maintenance duration was 3 hours. Ketamine infusion for 9 or 24 hours increased neuronal cell death in the frontal cortex, but no significant changes were noted in the hippocampus, thalamus, striatum, or amygdala. Cognitive impairments were observed beginning around 10 months of age, and persisted at 3.5 years of age.

The clinical studies will exclude neonates, infants, children, pregnant women, and breastfeeding women. Therefore, ketamine's neurotoxicity in juvenile animals does not represent a safety risk to eligible elderly subjects. Moreover, the large dosages and prolonged treatment durations associated with neurotoxicity in juvenile animals do not suggest a concern.

Chronic treatment with ketamine at high dose levels affected the brain of adolescent monkeys, as evidenced by histopathologic lesions and functional impairment.

The neurotoxicity of ketamine in adult animals is also associated with high dose levels, in contrast to the relatively low dose levels of esketamine associated with antidepressant efficacy in humans. In single-dose and 14-day repeated-neurotoxicity studies with intranasally administered esketamine in rats, no histopathologic brain lesions were noted even upon high exposures, as achieved at 54 mg/day in the 14-day study. In the 6-month rat and 9-month dog repeat-dose toxicology studies with intranasally administered esketamine, where the animals were of

adolescent age at initiation of treatment, and in the pre- and post-natal developmental toxicity study in rats, no evidence of neurotoxicity was found. Consequently, the risk of neurotoxicity associated with intranasal administration of esketamine to adult and adolescent patients is considered low.⁴²

Abuse Potential

Animal studies with ketamine suggest that it would have abuse potential in humans. These studies included self-administration and withdrawal experiments in several species.⁴²

Reproductive Toxicity

In a rat fertility and early embryonic developmental toxicity study with intranasally administered esketamine, no adverse effects on fertility or reproductive capacity or performance were found.

Rat and rabbit embryo-fetal developmental toxicity studies with intranasally administered racemic ketamine did not reveal evidence of reproductive toxicity. However, when monkey fetuses were exposed in utero to high dose levels of racemic ketamine, neurotoxicity was observed.

Intranasally administered esketamine did not affect pre- and postnatal development in rats. However, high dose levels of racemic ketamine induced neurotoxicity in early postnatal rat pups.⁴²

Considering the neurotoxic potential of ketamine and esketamine; and the fact that no threshold for these effects has been demonstrated, female subjects of childbearing potential should be adequately protected from becoming pregnant and pregnant women should not be enrolled.

Cardiovascular toxicity

In guinea pig tissues, ketamine-induced negative inotropic effects and shortening of action potential duration at the 0-mV level was observed, likely as a result of the suppression of inward calcium current, whereas in rat left atria and ketamine-induced positive inotropic effects and prolongation of action potential duration at the 0-mV level was observed, likely as a result of a decrease in calcium-insensitive transient outward current.²⁷ The inhibitory action on membrane currents may partly explain the species and tissue differences in inotropic responses to ketamine.

Blood pressure responses to ketamine also vary with the laboratory species and with experimental conditions. Blood pressure is increased in normotensive and renal hypertensive rats with and without adrenalectomy and under pentobarbital anesthesia. The US prescribing information for the anesthetic Ketalar (ketamine HCl for injection) provides the following guidance.⁴⁵

Intravenous Ketalar produces a fall in arterial blood pressure in the Rhesus monkey and a rise in arterial blood pressure in the dog. In this respect the dog mimics the cardiovascular effect observed in man. The pressor response to Ketalar injected into intact, unanesthetized dogs is accompanied by a tachycardia, rise in cardiac output and a fall in total peripheral resistance. It causes a fall in perfusion pressure following a large dose. The tachycardia and increase in

myocardial contractile force seen in intact animals does not appear in isolated hearts. These observations support the hypothesis that the hypertension produced by Ketalar is due to selective activation of central cardiac stimulating mechanisms leading to an increase in cardiac output.

The dog would be considered the most predictive species in terms of ketamine's cardiovascular effects in humans, but the antidepressant effects of ketamine were studied only in rodent models. The myocardial contractility effects and blood pressure responses to ketamine vary between species.⁴² Consequently, a margin of safety could not be reliably derived from the available animal data.

Overall Conclusion

The currently available nonclinical safety studies support chronic intranasal administration of esketamine in human subjects up to a dosage of 84 mg/day.

Further details can be found in the Investigator's Brochure.⁴²

1.1.2. Clinical Studies

1.1.2.1. Pharmacokinetics and Product Metabolism

Metabolism and Excretion

Ketamine and esketamine undergo extensive metabolism by hepatic cytochrome P450 (CYP). In humans, N-demethylation to norketamine is the major route of metabolism, which can undergo further metabolism to form hydroxynorketamine. Ketamine and norketamine are extensively hydroxylated to a series of 6 hydroxynorketamine metabolites and 2 hydroxyketamine metabolites.⁹⁴ Like ketamine, norketamine is a noncompetitive antagonist at the NMDA receptor.^{26,39} Norketamine has a half-life in plasma of approximately 5 hours.³⁷ The major human hepatic CYPs that catalyze ketamine N-demethylation in vitro are CYP2B6 and CYP3A4.^{38,68,96} The CYP enzymes responsible for the formation of norketamine metabolites include CYP2A6 and CYP2B6.⁶⁸ Published results of a clinical pharmacokinetic (PK) study indicate that esketamine does not invert to the R-enantiomer.³⁴ Racemic ketamine and its metabolites have been previously shown to be predominantly excreted in the urine. An average of 91% and 3% of a tritium-labeled dose (1 mg/kg) administered to 6 healthy subjects was recovered in urine and feces, respectively.⁶ Less than 3% of an administered dose was excreted in urine as parent drug.⁹³

A summary of the PK of esketamine administered by the IV and intranasal routes is provided below.

Intravenous Esketamine

Subjects with TRD received 0.2 mg/kg or 0.4 mg/kg esketamine as a 40-minute IV infusion during Study ESKTIVTRD2001.¹² Maximum concentrations of esketamine were observed at the end of the infusion. Mean maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) values increased with an increase in the esketamine dose administered (80.9 and 135 ng/mL, respectively, and 150 and 218 ng*h/mL, respectively, for 0.2 mg/kg and 0.4 mg/kg esketamine). The mean plasma clearance of esketamine was high

(109 L/h and 141 L/h for the 0.2 mg/kg and 0.4 mg/kg doses, respectively), as it was similar to or exceeded hepatic blood flow in humans.¹⁶ The large volume of distribution suggests that esketamine distributes widely into tissues (236 L and 303 L, respectively). The half-life of esketamine in plasma was 2.14 and 2.65 hours, respectively, for the 2 doses.

Intranasal Esketamine

Plasma esketamine PK results from Studies ESKETINTRD1001, ESKETINTRD1002, ESKETINTRD1003, and the double-blind phase of Panel A of the ESKETINTRD2003 that inform dose selection for the Phase 3 program are described below. The results demonstrate that plasma esketamine concentrations produced by effective IV regimens (0.2 mg/kg and 0.4 mg/kg as 40-minute infusions) may be achieved by the intranasal route.

Study ESKETINTRD1001 included 3 cohorts of subjects who were healthy male and female subjects.⁶ The intranasal esketamine treatments were self-administered under the direct supervision of the investigator or designee. Subjects in Cohorts 1 and 3 received esketamine doses that ranged from 28 to 112 mg. The regimens were self-administered in the upright position. No instructions were given with regard to sniffing after administration. The reported median time to reach C_{max} (T_{max}) of esketamine ranged from 0.37 to 0.83 hours from the time the first spray was administered (ie, 0.33 to 0.5 hours after the last spray was administered). The doses of 28 to 112 mg produced mean C_{max} values ranging from 63.3 to 151 ng/mL, while mean AUC_{∞} values ranged from 164 to 565 ng*h/mL. Mean C_{max} and AUC values of esketamine increased in a less than dose-proportional manner across the dose regimens. Furthermore, there was substantial overlap in the range of individual C_{max} and AUC values among the 3 doses. The mean terminal half-life of esketamine ranged from 5.86 to 9.83 hours across all treatments.

Subjects in Cohort 2 received 84 mg in a semi-reclined position and were instructed to sniff after each spray. Higher mean C_{max} and AUC_{∞} values were observed in this cohort (174 ng/mL and 453 ng*h/mL, respectively) compared with the same esketamine dose self-administered by subjects in Cohort 1 (107 ng/mL and 400 ng*h/mL, respectively). The semi-reclined position of the head and the instruction to subjects to sniff gently following intranasal dosing are believed to be the cause for the increase in exposure observed in Cohort 2 compared with Cohort 1. As a result, the instructions for self-administration of intranasal esketamine were adapted to include the semi-reclined position of the head and sniffing following dosing for all future studies.¹⁰

During the Phase 1 study ESKETINTRD1002, healthy Japanese and Caucasian subjects received single intranasal doses of esketamine 28 mg, 56 mg, and 84 mg in a crossover manner.¹⁰ On average, plasma esketamine C_{max} and AUC values were up to 48% higher in Japanese subjects as compared with Caucasian subjects.

Study ESKETINTRD1003 compared the PK, safety, and tolerability of intranasally administered esketamine in healthy elderly (≥ 65 years of age) and younger adult subjects (18 to 55 years of age, inclusive).¹¹ Subjects received a single intranasal treatment of esketamine 28 mg. Median time to reach the maximum plasma concentration (t_{max}) of esketamine was approximately 30 minutes for both age groups. The geometric means of the C_{max} and area under the plasma concentration-time curve from time 0 to infinite time, AUC_{∞} , for esketamine were

approximately 21% and 17% higher, respectively, in the elderly compared with younger adult subjects.¹¹

Study ESKETINTRD1012 evaluated the pharmacokinetics and safety of a single intranasal 84-mg dose, which was self-administered by 8 healthy subjects who were ≥ 75 years of age and 8 healthy younger adults (18 to 55 years of age).⁸ Preliminary data showed the median time to reach the maximum plasma concentration (t_{max}) of esketamine was 0.53 hours and 0.83 hours, in healthy elderly subjects ≥ 75 years of age and younger adults, respectively. The means of the C_{max} and area under the plasma concentration-time curve from time 0 to infinite time (AUC_{∞}), for esketamine were approximately 48% and 31% higher, respectively, in the elderly compared with younger adult subjects. Differences were greater based on median C_{max} and AUC_{∞} values (97% and 63% higher in the elderly, respectively).

Study ESKETINTRD2003 is an ongoing 2-panel, doubly randomized, double-blind, placebo-controlled, multicenter study.⁷⁰ Panel A was conducted in the United States and Belgium and Panel B in Japan. Panel A assessed the efficacy and safety of 3 dose strengths of intranasal esketamine (28, 56, and 84 mg) administered twice a week in subjects with TRD. Panel B (ongoing) is designed to assess the efficacy and safety of 14-mg and 56-mg dose strengths. Results of a preliminary analysis of data from the double-blind phase of Panel A indicate mean (standard deviation) esketamine concentrations at 40 minutes postdose were 36.4 ng/mL (16.4), 58.1 ng/mL (24.5), and 72.5 ng/mL (34.2), respectively, for the 3 doses. The mean esketamine concentrations in plasma samples collected on Days 1 and 11 were similar, suggesting that the PK results are consistent after repeated administration.

1.1.2.2. Pharmacodynamics and Efficacy

The efficacy of subanesthetic doses (0.5 mg/kg IV administered over 40 minutes) of IV ketamine has been evaluated in approximately 192 subjects with MDD (cases and controls), and in 2 studies in bipolar depressed subjects (meta-analyses).³³ This recently published meta-analysis of studies suggests that ketamine has a rapid onset (within 1 day) of antidepressant efficacy, including in those who have not benefitted from other antidepressant treatments, used as monotherapy or in combination with oral antidepressant treatments.

Esketamine (0.2 and 0.4 mg/kg administered over 40 minutes) has similar, rapid, and robust antidepressant effect as that seen with IV ketamine. A double-blind, double-randomization, placebo-controlled study (ESKETIVTRD2001) enrolled 30 adult subjects with TRD: 10 in the IV placebo group, 9 in the IV esketamine 0.20-mg/kg group, and 11 in the IV esketamine 0.40-mg/kg group (based on Day 1 randomization).¹² The full analysis set (FAS) of the primary efficacy variable (change in Montgomery-Asberg Depression Rating Scale [MADRS] total score from baseline Day 1 to Day 2) indicated that the improvement in both esketamine dose groups was statistically significant (1-sided p-value=0.001 in both dose groups) compared with the placebo group. The mean (standard deviation) change from baseline Day 1 to Day 2 in MADRS total score was -4.9 (4.72) in the placebo group, -16.8 (10.12) in the esketamine 0.20-mg/kg group, and -17.8 (9.45) in the esketamine 0.40-mg/kg group.

The studies listed above assessed the efficacy of ketamine or esketamine after a single dose as the primary endpoint. The average duration of response to a single dose of ketamine (0.5 mg/kg) was approximately 5 days. An open-label study demonstrated that the response to the first dose could be maintained by multiple infusions 3 times a week over 2 weeks. The duration of response lasted for approximately 19 days.¹

The KETIVTRD2002 study assessed whether multiple doses of ketamine given twice a week would also maintain the antidepressant response; the data from this study suggest that ketamine (0.50 mg/kg IV over 40 minutes) administered twice a week was sufficient for maintaining the initial effect over a 4-week treatment period.¹³

As noted above, Study ESKETINTRD2003 is a 2-panel, doubly randomized, double-blind, placebo-controlled, multicenter study.⁷⁰ Panel A was conducted in the United States and Belgium and Panel B in Japan. Panel A assessed the efficacy and safety of 3 dose strengths of intranasal esketamine (28, 56, and 84 mg) administered twice a week in subjects with TRD. Panel B (ongoing) is designed to assess the efficacy and safety of 14-mg and 56-mg dose strengths. In Panel A, subjects in period 1 (1-week duration) were randomly assigned in a 3:1:1:1 ratio to placebo (33 subjects), esketamine 28 mg (11 subjects), esketamine 56 mg (11 subjects), or esketamine 84 mg (12 subjects). An initial analysis of the data from the double-blind phase of Panel A indicates that of the 67 subjects randomized in Period 1, 63 entered Period 2 (1-week duration), in which 28 placebo subjects who were eligible for re-randomization at the end of Period 1, were randomly assigned in a 1:1:1:1 ratio to placebo (N=6), esketamine 28 mg (N=8), esketamine 56 mg (N=9), or esketamine 84 mg (N=5). Subjects eligible for re-randomization had to have a Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR₁₆) total score >11 at the end of Period 1.

The improvement (with respect to change in MADRS total score from baseline Day 1 to Day 8) in all 3 esketamine dose groups reached statistical significance ($p=0.021$, $p=0.001$, and $p<0.001$ for esketamine 28 mg, 56 mg, and 84 mg, respectively) compared with placebo. The results of the 2 periods were consistent. The mean differences from placebo on Day 8 (after 1 week of treatment), estimated using data from the combined periods, were:

- Esketamine 28 mg: -4.2 (SE 2.09)
- Esketamine 56 mg: -6.3 (SE 2.07)
- Esketamine 84 mg: -9.0 (SE 2.13)

The Cohen's D effect sizes in Period 1 for esketamine compared with placebo were:

- Esketamine 28 mg: low, 0.43 (CI -0.259-1.118)
- Esketamine 56 mg: high, 0.92 (CI 0.201-1.621)
- Esketamine 84 mg: high, 1.19 (CI 0.473-1.883)

The duration of effect with the 28-mg dose appears to be shorter, with the MADRS total score higher on Day 8 than on Day 2. The duration of effect for the 56- and 84-mg doses appears to support twice-a-week dosing.

These data with intranasal esketamine support the hypotheses that intranasal esketamine is effective as a treatment for depressive symptoms, that it has rapid onset of effect (typically within 2 hours), and that multiple repeated sessions dose-dependently show sustained response throughout the study duration. A clear dose response was seen in the double-blind data in Panel A, and the point estimates and confidence intervals suggest a high effect size (Cohen's D) with the 56-mg and 84-mg dose groups, supporting further development. Based on PK data from ESKETINTRD1012 it is also possible that the 28-mg dose in the elderly may overlap with the 56 mg dose in younger patients, so addition of the 28-mg dose in the elderly may provide an efficacious dose while improving safety.

1.1.2.3. Safety and Tolerability

Ketamine is a rapidly acting general anesthetic that is approved and widely used intravenously or intramuscularly for the induction and maintenance of anesthesia in children and adults at a dose of 1 to 3 mg/kg given as a bolus. Ketamine is marketed as a racemic mixture and in Europe also as the S-enantiomer, esketamine. Ketamine was first introduced as an anesthetic in 1963 and is considered to have an excellent medical safety profile (Ketalar[®] USPI 2012; Ketanest[®]S Summary of Product Characteristics [SmPC] 2011).^{36,45,46,71,84}

In the US prescribing information for ketamine HCl for injection and the SmPC for esketamine HCl for injection, the following adverse reactions were listed as very common, common, or frequent occurrences: Emergence or recovery reactions, elevated blood pressure and pulse rate, stimulation of respiration, nausea, and vomiting. See [Table 1](#) for details.

Table 1: Adverse Reactions Listed as Very Common, Common, or Frequent Occurrences in the Product Information of Anesthetic Ketamine and Esketamine

System Organ Class	"Frequent" Adverse Reactions Per Anesthetic Ketamine USPI ^{45,a}	"Very Common" or "Common" Reactions Per Anesthetic Esketamine SmPC ^{89,b}
Psychiatric disorders	<u>Frequency:</u> Emergence reactions occurred in approximately 12% of patients. <u>Characteristics:</u> Severity varied from pleasant dreamlike states, vivid imagery, hallucinations, and emergence delirium. Some states were accompanied by confusion, excitement, and irrational behavior, which some patients recalled as an unpleasant experience.	<u>Frequency:</u> Recovery reactions were common. When esketamine was the sole anesthetic, up to 30% of patients displayed dose-dependent recovery reactions. <u>Characteristics:</u> Reactions included vivid dreams (including nightmares), nausea and vomiting, increased salivation, blurred vision, dizziness, and motor restlessness ^c
Cardiac disorders	Blood pressure and pulse rate were frequently elevated after administration. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.	Common occurrences were temporary tachycardia and increase in blood pressure and heart rate (approximately 20% of the initial value was typical).
Respiratory, thoracic, and mediastinal disorders	Although stimulation of respiration was a frequently observed effect, severe depression of respiration or apnea also could occur after rapid intravenous administration of high doses.	Common effects were increase in vascular resistance in pulmonary circulation and increase in mucus secretion. Increased oxygen consumption, laryngospasms, and temporary respiratory depression were common; the risk of respiratory depression was noted to depend on dose and injection speed.
Gastro-intestinal disorders	No gastrointestinal effects were listed as frequent, but the USPI stated that anorexia, nausea, and vomiting have been observed.	Common effects included nausea and vomiting.

Abbreviations: SmPC, Summary of Product Characteristics; USPI, United States Prescribing Information

a. "Frequent" was not defined numerically, except in the case of emergence reactions (12%). The terms "very common" and "common" did not appear in the adverse effects section of the USPI.

b. "Very common" was defined in the SmPC as $\geq 1/10$ and "common" was defined as $\geq 1/100$ to $< 1/10$.

c. The incidence of these events can be greatly reduced by the administration of a benzodiazepine.

Source: Investigator's Brochure for esketamine (JNJ-54135419).⁴²

Adverse Events Associated with Short-term Use of Intranasal Esketamine in Patients with MDD

According to the SmPC for the esketamine solution for injection/infusion⁴⁴, the following are reported as common adverse effects: transient tachycardia, vivid dreams (including nightmares), nausea and vomiting, increased blood pressure, increased salivation, blurred vision, dizziness, motor unrest, increase in vascular resistance in pulmonary circulation and increase in mucus secretion, increased oxygen consumption, laryngospasms, and temporary respiratory depression. It is reported that the risk of respiratory depression typically depends on the dosage and injection speed.⁴⁴

Administration of esketamine is associated with a number of adverse events, which are transient in nature and typically resolve in 2 hours or less from the start of drug administration. The phase 1 study ESKETINTRD1003 evaluated the pharmacokinetics and safety of a single intranasal esketamine 28 mg in 14 healthy elderly subjects (≥ 65 years of age, with 3 subjects ≥ 75 years of age) and 20 healthy younger adult subjects (18 to 55 years of age, inclusive). The incidences of the treatment emergent adverse events (TEAEs) were slightly higher in young subjects (100% [20 subjects]) as compared with elderly subjects (85.7% [12 subjects]). The most commonly reported TEAEs by preferred term ($>20\%$) in elderly subjects were dysgeusia and vertigo (9 [64%], of 14 subjects each).¹¹

Additionally, another recently completed Phase 1 study, ESKETINTRD1012, evaluated the pharmacokinetics and safety of a single intranasal 84-mg dose, which was self-administered by 8 healthy elderly subjects who were ≥ 75 years of age (Cohort 1) and 8 healthy younger adults (18 to 55 years of age – Cohort 2). An initial review noted TEAEs occurred in all subjects in both cohorts (100% [16 subjects – 8 in each cohort]). The TEAE of illusions was reported in 5 younger subjects (62.5%) and in none of the elderly subjects. In elderly subjects, the incidence of TEAEs of vascular disorders (6 subjects [75%] including hot flush [2 subjects, 25%] and hypertension [3 subjects, 37.5%]) was higher than in younger adults (1 subject, 12.5% - hypertension). Vertigo and vertigo positional were more common in elderly subjects (5 subjects, 62.8% and 1 subject, 12.5%, respectively) than in younger adults (vertigo – 3 subjects, 37.5%).

In both cohorts, the maximal mean increase in systolic and diastolic blood pressure as well as heart rate was observed at 32 minutes post dose measurement time point. The mean increase in supine systolic blood pressure and pulse rate was slightly greater in Cohort 1 (Table 2) than in Cohort 2, while the mean increase in the supine diastolic blood pressure was greater in Cohort 2. In both Cohort 1 and Cohort 2, the mean systolic and diastolic blood pressure returned to baseline within 4 hours post dose.

Table 2: Mean Supine Blood Pressure and Heart Rate - Cohort 1 (ESKETINTRD1012)

Supine SBP (mm Hg)	Mean	Range	Mean Change	
			from Baseline	Range
Day 1, predose	133.5	104; 164		
Day 1, 32 min	165.3	141; 194	31.8	16; 44
Day 1, 50 min	154.1	127; 177	20.6	- 5; 38
Day 1, 1.5 h	145.6	123; 177	12.1	-11; 32
Day 1, 4 h	130.4	130; 170	-3.1	-36; 31
Supine DBP (mm Hg)				
Day 1, predose	68.0	54; 79		
Day 1, 32 min	81.5	64; 93	13.5	3; 20
Day 1, 50 min	77.1	65; 87	9.1	-3; 17
Day 1, 1.5 h	76.5	63; 81	8.5	-6; 14
Day 1, 4 h	68.5	57; 81	0.6	-16; 17
Supine Heart Rate (beats/min)				
Day 1, predose	60.0	48; 79		
Day 1, 32 min	74.8	53; 102	14.8	3; 38
Day 1, 50 min	70.9	53; 96	10.9	1; 32
Day 1, 1.5 h	62.9	46; 81	2.9	-7; 17
Day 1, 4 h	78.0	55; 97	18.0	-6; 39

Abbreviations: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure

In Panel A of the Phase 2 study with intranasal esketamine (ESKETINTRD2003), the most common TEAEs (>10% of subjects in the pooled esketamine treatment groups) during the double-blind phase were: dizziness, headache, dissociation, dysgeusia (metallic taste), nausea, dissociative disorder, and oral hypoesthesia.⁷⁸ Dissociative symptoms were the most typical of these adverse events observed postdose and were characterized by feeling unreal or detached

from reality or by perceptual changes. Transient perceptual changes (dissociation), dizziness, and nausea were typically seen immediately after drug administration, resolving by 2 hours.

No deaths were reported in the double-blind or open-label phases of the ESKETINTRD2003 study. One subject experienced an SAE of esophagitis in Panel A (double-blind phase, placebo/placebo treatment group). A total of 3 subjects withdrew during the double-blind phase because of adverse events. One subject in esketamine 28 mg group experienced a TEAE of syncope of severe intensity on Day 2 of Period 1, 1 day after receiving the first dose of study medication. The subject discontinued from the study and received no further study medication. The event resolved on the same day, and the investigator considered the event to be possibly related to the study agent. Another subject in the placebo/esketamine 56 mg group experienced a TEAE of headache of moderate intensity on Day 11 of Period 2. Study medication was stopped following this event, which resolved on the same day. The investigator considered the event to be very likely related to the study agent. A third subject in the esketamine group (84 mg/esketamine 84 mg) experienced a TEAE of dissociative disorder (verbatim term: Dissociative syndrome) of moderate intensity on Day 8 of Period 2 (day of the third esketamine 84 mg dose in the study). The subject discontinued from the study due to the event of dissociative disorder, which resolved on the same day. The investigator considered the event to be very likely related to the study agent.⁷⁸

In Panel A dissociative symptoms measured on the Clinician Administered Dissociative States Scale (CADSS) were dose-dependent and were observed to reduce significantly with multiple doses over 2 weeks. No psychotic symptoms were seen. Transient increases in mean blood pressure (systolic and diastolic) were observed post dose following the intranasal esketamine administration.

The mean (standard deviation; SD) peak systolic blood pressure after the first administration in each dose group in Panel A was:

- Placebo: 124.2 (11.51) mmHg; mean increase of 5.4 (7.84) mmHg
- Esketamine 28 mg: 131.8 (15.49) mmHg; mean increase of 10.4 (10.44) mmHg
- Esketamine 56 mg: 130.4 (18.64) mmHg; mean increase of 11.2 (15.01) mmHg
- Esketamine 84 mg: 146.1 (19.9) mmHg; mean increase of 17.1 (15.5) mmHg

Mean (standard deviation; SD) peak diastolic blood pressure after the first administration in each dose group was:

- Placebo: 81.2 (8.36) mmHg; mean increase of 3.8 (7.99) mmHg
- Esketamine 28 mg: 85.7 (9.16) mmHg; mean increase of 6.5 (7.00) mmHg
- Esketamine 56 mg: 86.5 (11.34) mmHg; mean increase of 7.2 (9.67) mmHg
- Esketamine 84 mg: 87.8 (10.62) mmHg; mean increase of 8.1 (9.12) mmHg

The blood pressure increase typically resolved within 2 hours. Unlike dissociative symptoms, the blood pressure changes observed do not appear to attenuate over time with multiple doses. Transient increases in heart rate were also observed in parallel with blood pressure change. There was no clinically meaningful change in blood oxygen level.

Adverse Events Associated with Chronic Use of Ketamine

There are no controlled studies of long-term use with esketamine/ketamine in patients with MDD. Much of the literature on chronic use of ketamine comes from data gathered from street/illegal use of the drug, rather than systematically conducted clinical studies. Data therefore should be interpreted with caution, as in many cases, no baseline pre-drug data are available and drug exposure is poorly documented.

In a 1-year longitudinal study, 150 subjects were divided into 5 groups of 30 subjects each. Frequent ketamine users (more than 4 times per week), infrequent ketamine users (at least once a month), abstinent users (abstinent for at least 1 month), polydrug controls, and non-users of illicit drugs.⁵⁷ Eighty percent of the participants were retested at the end of 1 year. Cognitive deficits (including impairment in spatial working memory, pattern recognition memory and category fluency) were mainly observed in frequent users and not with the infrequent users. Short-lasting, dose-dependent effects of psychosis were associated with ketamine users. There was no increase in symptoms over time, and symptoms were completely reversible upon stopping use of ketamine. As noted, these data should be interpreted with caution, as baseline data predating drug use were not available. Furthermore, in their recent review, Morgan and Curran report that there is little evidence of any link between chronic, heavy use of ketamine and diagnosis of a psychotic disorder.⁵⁶

The principal action of ketamine is at the NMDA receptor, and the consequences of ketamine use on cognition have been fairly widely investigated. Several studies have examined cognitive function in infrequent and frequent ketamine users.^{15,56,57,61} Overall, infrequent or recreational ketamine use does not appear to be associated with long-term cognitive impairment.⁵⁶ The most robust findings are that frequent ketamine users (more than 5 times a week) exhibit impairments in both short- and long-term memory.⁵⁴ Although dosages have varied, dosages reported by ketamine users in this study were much higher than the dosages of ketamine or equivalent doses of esketamine intended for use in treating TRD. Memory impairments may be reversible when individuals stop using the drug, as they were not found in a group of 30 ex-ketamine users who had been abstinent for at least a year.^{56,57}

Ketamine-induced ulcerative cystitis is a recently identified complication.⁵⁶ The most common symptoms are frequency and urgency of urination, dysuria, urge incontinence, and occasionally painful hematuria (blood in urine). Computerized tomography scans of these subjects revealed a marked thickening of the bladder wall, a small bladder capacity, and perivesicular stranding consistent with severe inflammation. At cystoscopy, all patients had severe ulcerative cystitis. Biopsies in 4 of these cases found denuded urothelial mucosa with thin layers of reactive and regenerating epithelial cells, and ulcerations with vascular granulation tissue and scattered inflammatory cells. Cessation of ketamine use provided some relief of symptoms. Most of the

described cases are in near-daily users of ketamine for recreational purposes. The prevalence is difficult to determine, as it is seen in recreational users who often do not seek help.

The majority of cases resolve after stopping ketamine use, one-third remaining static.

Abuse Liability, Dependence, and Withdrawal

There are a number of reports of ketamine dependence in the literature but no large-scale studies, and so the incidence of ketamine dependence is largely unknown.^{41,43,55,56,65} An interview study of 90 ketamine users found that 57% of frequent users, 43% of infrequent users, and 60% of ex-users expressed concerns about ketamine addiction.⁵⁹ The majority of frequent users in that study reported using the drug without stopping until supplies ran out, so compulsive patterns of behavior are also a concern. Oral ketamine has also been evaluated as a positive control in human abuse potential studies, with dosages of 65 mg and 110 mg reported as appropriate for use as positive controls for future abuse potential studies of compounds with a similar mechanism of action or with possible perception-altering effects.⁷⁹ There is conflicting evidence of the existence of a "withdrawal syndrome" after cessation of ketamine use.⁵⁶ Cravings seem to be a key problem in frequent users: 28 of the 30 daily users in 1 study reported having tried to stop taking the drug but failed; all reported ketamine cravings as the reason for failure.⁵⁶ The same study found that 12 of the 30 daily users reported withdrawal symptoms characterized by anxiety, shaking, sweating, and palpitations when they stopped using. A few published case studies also show craving and somatic and psychological aspects of anxiety as withdrawal symptoms.¹⁴ However, a specific ketamine withdrawal syndrome has not yet been described.⁵⁶

Please refer to the Investigator's Brochure for a summary of the adverse events reported in ketamine and esketamine studies.⁴²

1.1.3. Marketing Experience

No intranasal formulation of esketamine is currently marketed.

1.2. Active Comparators in Double-blind Induction Phase

This study will evaluate a flexible dose regimen of intranasal esketamine (28 mg, 56 mg or 84 mg) plus a newly initiated oral antidepressant, compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo.

In the double-blind induction phase, subjects will be assigned to receive 1 of 4 commercially available oral antidepressant medications from 2 different classes of antidepressant medications, selective serotonin reuptake inhibitors (SSRIs: Escitalopram or sertraline), or serotonin and norepinephrine reuptake inhibitors (SNRIs: Duloxetine or venlafaxine extended release [XR]).

The indications and safety information provided below for each oral antidepressant are from the USPI.^{24,28,81,87} For further information, please refer to the appropriate package insert applicable to the local country in which the study is being conducted.

In the US, all of the oral antidepressant options include a black box warning in the prescribing information regarding suicidality and antidepressant drugs. The black box warning informs the prescriber that antidepressant treatments increased the risk, as compared with placebo, of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of MDD and other psychiatric disorders. It states that anyone considering using the antidepressant in this population must balance the risk with the clinical need. Refer to the US prescribing information for the entire content of the black box warning.^{24,28,81,87}

1.2.1. Selective Serotonin Reuptake Inhibitors

1.2.1.1. Escitalopram

Escitalopram is indicated in adults for acute and maintenance treatment of MDD and acute treatment of generalized anxiety disorder.²⁸

The starting dosage for MDD in the USPI is 10 mg once daily with a maximum of 20 mg once daily. If the dosage is increased to 20 mg, this should occur after a minimum of 1 week. No additional benefits have been seen at 20 mg/day dose; 10 mg/day is the recommended dose for most elderly patients and this is the maximum dose that will be used in the current study.

In adult MDD subjects treated with escitalopram, the most commonly observed adverse reactions with escitalopram (incidence of approximately 5% or greater and approximately twice the incidence in placebo subjects) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence.

Contraindications to the use of escitalopram include serotonin syndrome and monoamine oxidase inhibitor (MAOI) use (concomitant use with MAOIs intended to treat psychiatric disorders, linezolid, or IV methylene blue; use within 14 days of stopping treatment with an MAOI intended to treat psychiatric disorders [in addition, an MAOI should not be used within 14 days of stopping escitalopram]); concomitant use with pimozide; and known hypersensitivity to escitalopram or citalopram or any of the inactive ingredients.

As with most SSRIs, a gradual reduction in the dosage rather than abrupt cessation of escitalopram treatment is recommended whenever possible.

1.2.1.2. Sertraline

Sertraline HCl is indicated in adults for the treatment of MDD, obsessions and compulsions in patients with obsessive compulsive disorder, panic disorder (with or without agoraphobia), post-traumatic stress disorder, premenstrual dysphoric disorder, and social anxiety disorder.⁸¹

According to the US prescribing information, sertraline should be administered at a dose of 50 mg once daily for the treatment of MDD. While a relationship between dose and effect has not been established for MDD, obsessive compulsive disorder, panic disorder, post-traumatic stress disorder, or social anxiety disorder, patients were dosed in a range of 50-200 mg/day in the clinical trials demonstrating the effectiveness of sertraline for the treatment of these indications. Consequently, a dose of 50 mg, administered once daily, is recommended as the initial

therapeutic dose. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Dose adjustment is recommended in the elderly.

In the current study, to improve tolerability, an initial starting dose of 25 mg is used based on experience in clinical practice with elderly patients. Given the 24 hour elimination half-life of sertraline, dose changes should not occur at intervals of less than 1 week. In the current study, the highest dose is 150 mg/day and patients not tolerating higher doses of sertraline may have the dose reduced to a minimum of 50 mg/day.

Contraindications to the use of sertraline include serotonin syndrome and MAOI use (concomitant use with MAOIs intended to treat psychiatric disorders, linezolid, or IV methylene blue; use within 14 days of stopping treatment with an MAOI intended to treat psychiatric disorders); concomitant use with pimozide; and known hypersensitivity to sertraline or any of the inactive ingredients.

In adult subjects, the most common TEAEs associated with the use of sertraline (incidence of at least 5% for sertraline or at least twice that for placebo within at least one of the indications) were ejaculation failure, dry mouth, increased sweating, somnolence, tremor, dizziness, fatigue, pain, malaise, abdominal pain, anorexia, constipation, diarrhea/loose stools, dyspepsia, nausea, agitation, insomnia, and decreased libido.

As with most SSRIs, a gradual reduction in the dosage rather than abrupt cessation treatment is recommended whenever possible.

1.2.2. Serotonin and Norepinephrine Reuptake Inhibitors

1.2.2.1. Duloxetine

Duloxetine is indicated in adults for MDD, generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain.²⁴

The starting dosage for MDD in the USPI is 40 to 60 mg/day. The dosage for acute treatment is 40 to 60 mg/day, with maintenance treatment at 60 mg/day. A starting dose of 30 mg/day has also been evaluated.⁹¹ In the current study, for improved tolerability in an elderly patient population, the initial starting dose is 30 mg/day.

No dose adjustment is recommended for elderly patients on the basis of age. As with any drug, caution should be exercised in treating the elderly. When individualizing the dosage in elderly patients, extra care should be taken when increasing the dose. The maximum dosage is 120 mg/day, although there is no evidence that dosages greater than 60 mg/day confer any additional benefits. The maximum dose to be used in this study is 60 mg/day.

For pooled studies for all approved indications, the most commonly observed adverse reactions in duloxetine-treated subjects (incidence of at least 5% and at least twice the incidence in placebo subjects) were nausea, dry mouth, somnolence, fatigue, constipation, decreased appetite, and hyperhidrosis. As observed in diabetic peripheral neuropathy studies, duloxetine treatment worsens glycemic control in some subjects with diabetes.

Contraindications to the use of duloxetine include use of an MAOI concomitantly or within 2 weeks of MAOI use; and use in patients with uncontrolled narrow-angle glaucoma

A gradual reduction in the dosage rather than abrupt cessation is recommended whenever possible.

1.2.2.2. Venlafaxine Extended-release

Venlafaxine XR is indicated in adults for MDD and social anxiety disorder.⁸⁷

The starting dosage for MDD in the USPI is 75 mg/day (in some patients, 37.5 mg/day for 4 to 7 days), with a dosage increase by 75 mg/day at intervals of 4 days or longer, and a maximum dosage of 225 mg/day. No dose adjustment is recommended for the elderly on the basis of age alone, although other clinical circumstances, some of which may be more common in the elderly, such as renal or hepatic impairment.

Dosage reductions are recommended for hepatic impairment (including mild) and renal impairment. In the current study, the starting dose of venlafaxine is 37.5 mg and the maximum dose attained is 150 mg based on the 4 week double-blind treatment duration. Patients not tolerating higher doses of venlafaxine XR may have the dose reduced to a minimum of 75 mg/day.

Contraindications to the use of venlafaxine XR include serotonin syndrome and MAOI use (concomitant use with MAOIs intended to treat psychiatric disorders, linezolid, or IV methylene blue; use within 14 days of stopping treatment with an MAOI intended to treat psychiatric disorders); concomitant use with pimozide; and known hypersensitivity to venlafaxine XR or any of the inactive ingredients.

In adult subjects with MDD, adverse events in short-term studies that occurred in at least 5% of the subjects receiving venlafaxine XR capsules and at a rate at least twice that of the placebo group were abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, and anorexia), central nervous system complaints (dizziness, somnolence, and abnormal dreams), and sweating.

Sustained hypertension is noted within the Warnings and Precautions section. Preexisting hypertension should be controlled before treatment with venlafaxine XR. It is recommended that patients receiving venlafaxine XR tablets have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure while receiving venlafaxine XR, either dosage reduction or discontinuation should be considered.

Across most indications, a dose-related increase in supine systolic and diastolic blood pressure was evident in venlafaxine XR-treated patients. Across all clinical studies, 1.4% of subjects in the venlafaxine XR-treated groups experienced a ≥ 15 mmHg increase in supine diastolic blood pressure, with blood pressure ≥ 105 mmHg, compared with 0.9% of subjects in the placebo groups. Similarly, 1% of subjects in the venlafaxine XR-treated groups experienced a ≥ 20 mmHg increase in supine systolic blood pressure, with blood pressure ≥ 180 mmHg, compared with 0.3% of subjects in the placebo groups.

A gradual dosage reduction, individualized as necessary, is recommended to avoid discontinuation symptoms.

1.3. Overall Rationale for the Study

This study is being conducted to evaluate the efficacy, safety, and tolerability of flexibly dosed intranasal esketamine (28 mg, 56 mg or 84 mg) plus a newly initiated oral antidepressant in elderly subjects with TRD. The study will serve as a pivotal Phase 3 short-term efficacy and safety study in support of regulatory agency requirements for registration of intranasal esketamine for the treatment of TRD.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective of this study is to evaluate the efficacy of switching elderly subjects with TRD from a prior antidepressant treatment (to which they have not responded) to flexibly-dosed intranasal esketamine (28 mg, 56 mg or 84 mg) plus a newly initiated oral antidepressant compared with switching to a newly initiated oral antidepressant (active comparator) plus intranasal placebo, in improving depressive symptoms, as assessed by the change from baseline in the MADRS total score from Day 1 (pre-randomization) to the end of the 4-week double-blind induction phase.

Secondary Objectives

- To assess the effect of intranasal esketamine plus a newly initiated oral antidepressant compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo on the following parameters in elderly subjects with TRD:
 - Depression response rates,
 - Depression remission rates,
 - Overall severity of depressive illness,
 - Health-related quality of life and health status.
- To investigate the safety and tolerability of intranasal esketamine plus a newly initiated oral antidepressant compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo in elderly subjects with TRD, including the following parameters:
 - Treatment-emergent adverse events (TEAEs), including TEAEs of special interest
 - Local nasal tolerability
 - Effects on heart rate, blood pressure, respiratory rate, and blood oxygen saturation
 - Effects on alertness and sedation
 - Potential psychosis-like effects
 - Dissociative symptoms

- Potential effects on cognitive function
- Potential effects on suicidal ideation/behavior
- Potential treatment-emergent symptoms of cystitis and/or lower urinary tract symptoms
- Potential withdrawal and/or rebound symptoms following cessation of intranasal esketamine treatment
- Potential effects on sense of smell
- To assess the PK of intranasal esketamine in elderly subjects with TRD receiving intranasal esketamine plus a newly-initiated oral antidepressant.

Exploratory Objectives

- To assess the pharmacokinetic/pharmacodynamic (PK/PD) relationship of intranasal esketamine and MADRS total score in elderly subjects with TRD.
- To assess the potential relationship of biomarkers with response/nonresponse to intranasal esketamine or oral antidepressants in elderly subjects with TRD.

2.2. Hypothesis

The hypothesis for this study is that, in elderly subjects with TRD, switching from a failed antidepressant treatment to intranasal esketamine plus a newly initiated oral antidepressant is superior to switching to a newly initiated oral antidepressant treatment (active comparator) plus intranasal placebo in improving depressive symptoms.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind, active-controlled, multicenter study in male and female elderly subjects with TRD to assess the efficacy, safety, and tolerability of flexibly dosed intranasal esketamine (28 mg, 56 mg or 84 mg) plus a newly initiated oral antidepressant, compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo. The study has 3 phases which are briefly described below.

Screening/prospective observational phase (4-week duration + optional 3-week taper period)

- This phase will prospectively assess treatment response to the subject's current oral treatment regimen. At the start of the screening/prospective observational phase, the subject must have had documented nonresponse to at least one antidepressant treatment (based on MGH-ATRQ criteria) in the current episode of depression, and the subject is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other ongoing medications being taken for depression at screening (including adjunctive/augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4. After 4

weeks, subjects who are nonresponders to their current oral antidepressant treatment (as assessed by independent, remote raters) may be eligible to proceed to the double-blind induction phase. Non-response at the end of the screening/prospective observational phase is defined as $\leq 25\%$ improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥ 24 on Week 2 and Week 4.

- Eligible subjects who are entering the double-blind induction phase will discontinue all of their current antidepressant treatment(s), including adjunctive/augmentation therapies. Of note, subjects taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening/prospective observational phase can continue these medications. No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepines are permitted during the screening/prospective observational phase. If clinically indicated, a subject's current antidepressant treatment(s) may be tapered and discontinued over an additional, optional period of up to 3 weeks per the local prescribing information or per clinical judgment. This 3 week period may also be used to optimize medical management if needed to facilitate subject participation (eg, treatment of blood pressure or diabetes, wean from other medications, etc.). In such cases, if there is no planned taper, the oral regimen should be continued in the interim and then discontinued by Day 1 of the double-blind induction phase.
- As a new oral antidepressant will be initiated on Day 1 of the double-blind induction phase, eligible subjects who do not require a tapered discontinuation of their antidepressant treatment(s) can proceed immediately into the double-blind induction phase.

Double-blind induction phase (4-week duration)

- Approximately 148 eligible subjects will be randomly assigned at a 1:1 (n=74 subjects per treatment arm) to receive double-blind intranasal treatment with either esketamine (28 mg, 56 mg or 84 mg) or placebo. Starting with a dose of 28 mg on Day 1, the intranasal treatment sessions (esketamine or placebo) will occur twice weekly for 4 weeks. In addition, all subjects will initiate a new, open-label oral antidepressant on Day 1 that will be taken daily for the duration of the induction phase. The assigned oral antidepressant will be 1 of 4 oral antidepressant medications (duloxetine, escitalopram, sertraline, or venlafaxine XR) that the subject has not previously had a nonresponse to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country.
- Subjects taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening/prospective observational phase can continue these medications during the induction phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the induction phase, with the exception of the use of permitted benzodiazepine rescue medication.
- At the end of the double-blind induction phase, regardless of response status, subjects may be eligible to participate in the subsequent study ESKETINTRD3004 if they meet all other study entry criteria. ESKETINTRD3004 is a long-term open-label safety study involving repeated treatment sessions of intranasal esketamine.

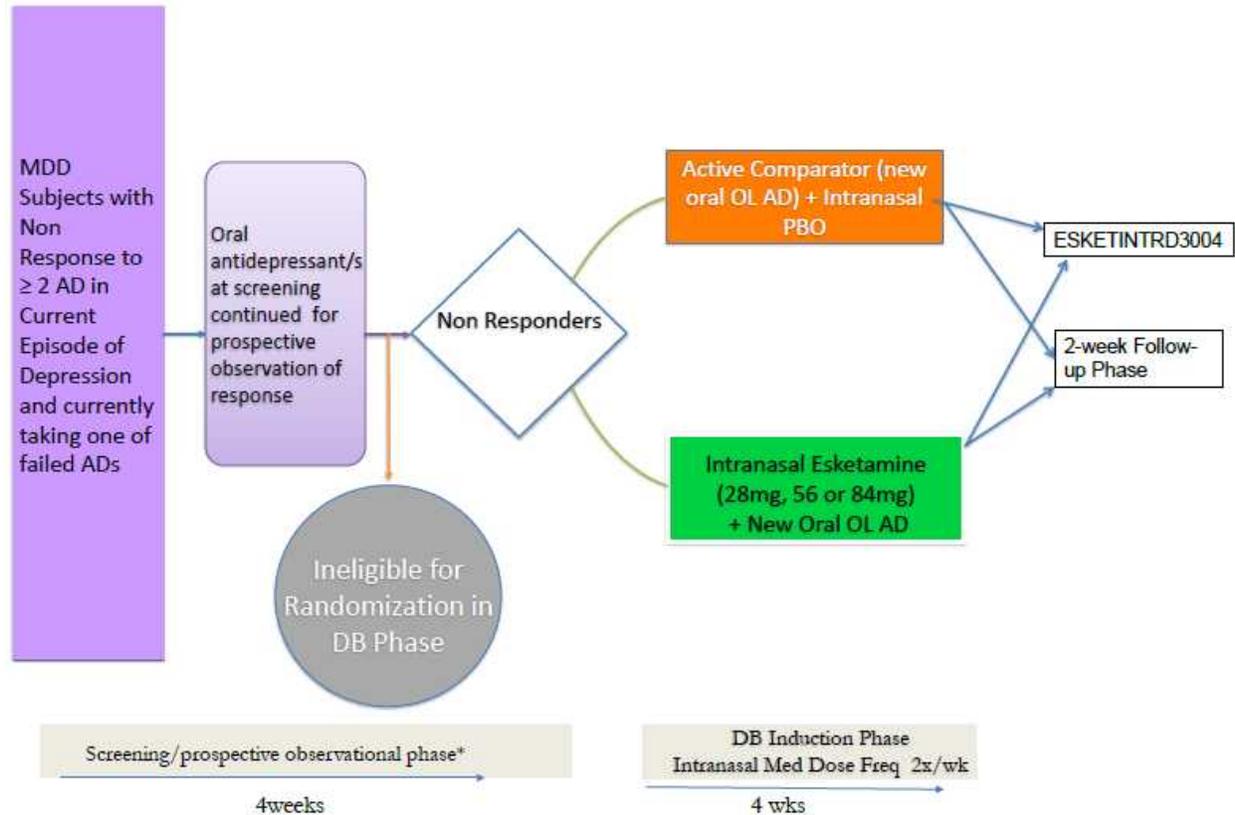
- If a subject withdraws from the study before the end of the double-blind induction phase for reasons other than withdrawal of consent, an Early Withdrawal visit should be conducted within 1 week of his/her discontinuing from the study, followed by the follow-up phase.

Follow-up phase (2-week duration)

- This phase will include all subjects who withdraw early before the end of the double-blind induction phase, or choose not to participate in the subsequent ESKETINTRD3004 safety study, and have received at least 1 dose of intranasal study medication in the double-blind induction phase. There will be no intranasal treatment sessions administered during this phase.
- At the start of the follow-up phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the subject's treating physician. All subjects will be provided with an additional 2-week supply of the oral antidepressant medication to ensure that there is no interruption of oral antidepressant therapy during the transition to further clinical/standard of care. The decision to continue the oral antidepressant in this phase will be at the discretion of the investigator, however, in order to better assess potential withdrawal symptoms from intranasal study medication the oral antidepressant medication should be continued for the 2 weeks of the follow-up phase unless determined as not clinically appropriate.

Taking into consideration the up to 3-week optional taper period, the duration of a subject's study participation will be 8 to 11 weeks (for subjects continuing into ESKETINTRD3004) or 13 weeks (for subjects completing the follow-up phase).

A diagram of the study design is provided in [Figure 1](#).

Figure 1: Study Design for ESKETINTRD3005

* followed by optional, up to 3 week Taper if clinically indicated.

AD=antidepressant. DB=double-blind. D/C=discontinued. Esk=Esketamine. MDD=major depressive disorder. OL=open-label. PBO=placebo.

Note: Subjects who withdraw early from the double-blind induction phase and receive at least 1 dose of intranasal study medication in the double-blind induction phase will have an Early Withdrawal visit performed and then proceed into the follow-up phase.

A planned interim analysis is described in Section 11.3.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study. Please refer to Section 11.9, Independent Data Monitoring Committee, for details.

3.2. Study Design Rationale

3.2.1. Study Population

The study population will include elderly men and women, therefore the lower age limit of 65 years (inclusive), is appropriate.

Subjects will meet Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-5) diagnostic criteria for single-episode MDD (if a single episode, duration of episode must be ≥ 2 years) or recurrent MDD, without psychotic features, based upon clinical assessment, and confirmed by the Mini-International Neuropsychiatric Interview (MINI). At the start of the screening/prospective observational phase, the subject must have an Inventory of Depressive

Symptomatology-Clinician rated, 30-item (IDS-C₃₀) total score of ≥ 31 , which corresponds to moderate to severe depression.

Treatment-resistant depression is defined as a lack of clinically meaningful improvement after treatment with at least 2 different antidepressant agents prescribed in adequate dosages for adequate duration. At the start of this study, subjects must have had nonresponse (defined as $\leq 25\%$ improvement) to ≥ 1 but ≤ 8 (if current episode is > 2 years, upper limit applicable to only the last 2 years) oral antidepressant treatments taken at adequate dosage and for an adequate duration, as assessed on the Massachusetts General Hospital–Antidepressant Treatment Response Questionnaire (MGH-ATRQ) and documented by records (eg, medical/pharmacy/prescription records, a letter from the treating physician, etc.) for the current episode of depression. Subjects who have had some initial response, but then lose the response (eg, tolerance effects/bradyphylaxis etc.), to an antidepressant treatment will not be considered to have failed that antidepressant treatment. The use of historical data to define nonresponse to treatment prior to patient enrollment in a treatment study is considered practical and valid. The MGH-ATRQ is a validated tool to assess treatment response.

In addition, at the start of the screening/prospective observational phase, the subject must be taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other medications being taken for depression at screening (including adjunctive/augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4.

Non-response at the end of the screening/prospective observational phase is defined as $\leq 25\%$ improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥ 24 on Week 2 and Week 4.

The subject's current major depressive episode, depression symptom severity (Week 1 MADRS total score ≥ 24 required), and antidepressant treatment response in their current depressive episode (retrospectively assessed) must be deemed valid for participation in the clinical study based on a Site Independent Qualification Assessment. The Site Independent Qualification Assessment is a tool to facilitate subject selection for MDD clinical studies, with a goal to ensure enrollment of subjects who have symptoms that reflect the current state of illness and that these symptoms can be reliably measured with appropriate measurement tools, as well as to minimize placebo response.

3.2.2. Study Phases

The 4-week duration of the screening/prospective observational phase will provide adequate time to assess subject eligibility according to the study entry criteria, while also allowing for a prospective confirmation of nonresponse to the current antidepressant treatment(s) that is continued for the duration of this phase. The dose of all antidepressant medication(s)/treatment(s) should remain unchanged throughout the screening/prospective

observational phase. This method of recruitment allows subjects to enter the study on a variety of different antidepressant medications that they had been taking, which mimics clinical practice and yet allows for prospective demonstration of treatment resistance to the current antidepressant treatment. Even though there is no depression rating score available at the start of the antidepressant treatment, the subjects at screening will have to meet criteria for moderate to severe depression.

After 4 weeks of prospective observation of continuation of the current antidepressant treatment and assessment of treatment response, subjects who meet the predefined nonresponse criteria and are eligible to enter the double-blind induction phase will discontinue all of the current antidepressant treatments, including adjunctive/augmentation therapies, prior to starting the next phase.

Nonresponders who are eligible to enter the double-blind induction phase are permitted to have up to 3 additional weeks to taper and discontinue their current antidepressant treatment prior to entry into the double-blind induction phase per the local prescribing information or clinical judgment (eg, tolerability concerns). The optional taper of up to 3 weeks is expected to provide an adequate amount of time for taper and discontinuation. This 3 week period may also be used to optimize medical management if needed to facilitate subject participation (eg, treatment of blood pressure or diabetes, wean from other medication, etc.). In such cases, if there is no planned taper, the oral regimen should be continued in the interim and then discontinued by Day 1 of the double-blind induction phase.

As described in Section 1.1.2, the duration of the 4-week double-blind induction phase was selected based upon the onset of effect of typical antidepressant treatments, with a 4 week duration considered to be sufficiently long to show the antidepressant effects of the active comparator. Preliminary findings from an analysis of antidepressant treatments were presented recently, as well as a completed analysis of 24 recent MDD studies that compared study durations of 4, 6, and 8 weeks. Exploratory analyses were conducted for each of the study durations using mixed-effects model for repeated measures (MMRM), but excluding data beyond the duration of interest. These preliminary findings suggest that it is plausible to shorten the study duration down to 4 weeks.^{48,97} Similarly, it has been demonstrated that improvement of $\geq 25\%$ on the Hamilton Depression 17-item Rating Scale (HDRS) on Day 14 was a significant cutoff value to predict response after 5 weeks of treatment and a lack of improvement (ie, $< 25\%$) by Day 14 predicted poor response after 5 weeks of treatment.⁶³ All together, these results suggest that a 4-week duration should be adequate to assess antidepressant response.

For subjects entering the follow-up phase, the 2-week duration following the last dose of intranasal study medication will allow sufficient time to assess safety and tolerability after cessation of intranasal study medication, including potential withdrawal symptoms. During this follow-up phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the subject's treating physician.

3.2.3. Blinding and Randomization

Blinded intranasal treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

An intranasal placebo control will be used in the double-blind induction phase to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of intranasal active treatment.

Randomization will be used to minimize bias in the assignment of subjects to intranasal treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. The randomization will be stratified by country and class of antidepressant (SNRI or SSRI) with an allocation ratio of 1:1 to intranasal placebo or intranasal esketamine. The stratification is aimed at balancing treatment groups across country and class of antidepressant.

3.2.4. Treatment Groups and Dose Selection

The 2 treatment groups in the double-blind induction phase are:

- Intranasal esketamine (28 mg, 56 mg or 84 mg)
- Intranasal placebo

Of note, to improve tolerability, subjects who are assigned to esketamine will start with 28 mg of intranasal esketamine on Day 1.

In all treatment groups, subjects will switch to a new, oral antidepressant, initiated on Day 1 of the double-blind induction phase, that will continue for the duration of the phase and longer, if applicable.

The treatment groups will allow for an evaluation of the efficacy, safety, and tolerability of flexibly dosed intranasal esketamine, plus a newly initiated oral antidepressant as compared with a newly initiated oral antidepressant treatment plus intranasal placebo as an active comparator in elderly subjects with TRD.

Intranasal Study Drug

The dose selection (28 mg, 56 mg and 84 mg) and administration interval (2 treatment sessions per week for 4 weeks) for this study were based on the sponsor's previous clinical data; in particular the results from Studies ESKETIVTRD2001, KETIVTRD2002, ESKETINTRD1001, ESKETINTRD1003, ESKETINTRD1012 and Panel A of the ESKETINTRD2003 study, described above in Section 1.1.2.

The data from Study ESKETINTRD2003 Panel A support the hypotheses that both the 56 mg and 84 mg doses are effective as a treatment for depression in subjects with TRD, that they have a rapid onset of effect, and that 2 treatment sessions per week can sustain the response throughout the 4 week duration of the double-blind induction phase. In addition, the 56 mg and

84 mg dosages were generally well tolerated by subjects. PK data from study ESKETINTRD1003 (CSR ESKETINTRD1003 in preparation) which evaluated intranasally administered esketamine in elderly (≥ 65 years of age) and younger adult subjects (18 to 55 years of age, inclusive), indicated plasma esketamine C_{max} and AUC values are relatively comparable between the elderly and younger adults.¹¹ More recently, Study ESKETINTRD1012 evaluated the pharmacokinetics and safety of a single intranasal 84 mg dose in elderly subjects ≥ 75 years of age. Preliminary data showed the means of the C_{max} and AUC_{∞} were approximately 48% and 31% higher, respectively, in the elderly compared with younger adult subjects. Differences were greater based on median C_{max} and AUC_{∞} values (97% and 63% higher in the elderly, respectively). Based on PK data from ESKETINTRD1012 it is also possible that the 28 mg dose in the elderly may overlap with the 56 mg dose in younger patients, so addition of the 28 mg dose in the elderly may provide an efficacious dose while improving safety.

In the current study, subjects who are randomly assigned to esketamine will start with 28 mg of intranasal esketamine on Day 1. The dose of esketamine may be maintained at 28 mg or increased to 56 mg on Day 4. On Day 8, 11 or 15 the dose may be maintained, increased or reduced by 28 mg, with no further increases in dose permitted after Day 15. The dose may be decreased by 28 mg on subsequent dosing days. The rationale for this approach is that using the lower starting dose (28 mg) initially and then adjusting the dose in increments of 28 mg based on efficacy and tolerability may allow subjects to adjust to the effects of the lower dose before going to higher doses. For example, internal data from the CADSS suggest a dose response, with the greatest effect seen initially on the 84 mg dose (ESKETINTRD2003). However, on subsequent repeated dosing, dissociative symptoms lessen. Starting with the lower dose may therefore limit the number of elderly subjects discontinuing the study treatment because of intolerance.

The use of flexible dosing, rather than using a fixed dose, of intranasal esketamine is considered to facilitate improved tolerability by gradually increasing to a higher dose and will also inform clinical practice, as many clinicians prefer to gradually increase, and then adjust as clinically required, the dose of an antidepressant medication in the elderly population.

Oral Antidepressant

On Day 1 of the double-blind induction phase, a new, open-label oral antidepressant treatment will be initiated in all subjects. Each subject will be assigned to receive 1 of 4 oral antidepressant medications from 2 different classes of antidepressant treatments, an SSRI (escitalopram or sertraline) or an SNRI (duloxetine or venlafaxine XR).

The assignment of the oral antidepressant treatment will be done by the investigator based on review of the MGH-ATRQ and relevant prior antidepressant medication treatment information.

These 2 classes were selected because they are the most commonly prescribed antidepressant classes in this population and are generally well-tolerated. The oral antidepressant treatment assigned will be one that the subject has not previously had a nonresponse to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country. Dosing of the oral antidepressant will begin on Day 1. A mandatory

titration schedule is provided (Attachment 3) to ensure that the oral antidepressant is taken at an adequate dosage and duration for efficacy assessment at the end of the double-blind induction phase as well as for potential maintenance of effect (in the subsequent ESKETINTRD3004 study). Doses are not to exceed the maximum dose defined in the titration schedule. If higher doses are not tolerated, a down-titration is permitted based on clinician's judgment.

3.2.5. Efficacy Measures

MADRS

The 10-item clinician-administered MADRS was designed to be used in subjects with MDD to measure the overall severity of depressive symptoms.^{53,54} The MADRS scale has been selected as the primary efficacy measure for this study because it is validated, reliable, and acceptable to regulatory health authorities as a primary scale to determine efficacy in major depression.

The primary efficacy endpoint is the change in the MADRS total score from baseline (Day 1 prior to randomization) to the end of the 4-week double-blind induction phase.

In this study, subjects in either of the 2 treatment groups who respond to the study medication (ie, responders) are defined as subjects who meet the criterion for response defined as $\geq 50\%$ reduction in the MADRS total score from baseline (Day 1 pre-randomization) to the end of the 4-week double-blind induction phase.

MADRS will also be used to evaluate a secondary objective assessing proportion of subjects with response and those in remission (defined as subjects with a MADRS total score ≤ 12) at the end of the 4-week double-blind induction phase.⁵⁰

Clinical Global Impression – Severity (CGI-S)

The CGI-S is included to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis and improvement with treatment.³⁵ Please refer to Section 9.2.1.2.1 for additional information regarding CGI-S.

EuroQol-5 Dimension-5 Level (EQ-5D-5L)

The EQ-5D-5L is included as a standardized patient-completed instrument for use as a measure of health-related quality of life and health status.^{27,31} Please refer to Section 9.2.1.3.1 for additional information regarding EQ-5D-5L.

3.2.6. Safety Evaluations

Physical examination, body weight, vital signs (including blood pressure measurements), 12-lead ECG, pulse oximetry, clinical laboratory tests, nasal examinations, and evaluation of TEAEs and concomitant therapies will be performed throughout the study to monitor subject safety.

TEAEs of special interest will be examined separately grouped in the following categories: drug abuse, dependence and withdrawal (standardized Medical Dictionary for Regulatory Activities

[MedDRA] queries [SMQ]), increased blood pressure, increased heart rate, transient dizziness/vertigo, impaired cognition, anxiety, and cystitis.

A subject-completed nasal symptom questionnaire will also be conducted as per the Time and Event Schedule to assess for any treatment-emergent nasal tolerability symptoms.

The Columbia Suicide Severity Rating Scale (C-SSRS)⁶⁹ will be performed to assess suicidal ideation and behavior, the CADSS will be administered to assess treatment-emergent dissociative symptoms, the BPRS+ will be administered to assess treatment-emergent psychotic symptoms, the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) will be used to measure treatment-emergent sedation, the Clinical Global Assessment of Discharge Readiness (CGADR) will be used to measure the subject's readiness for discharge based on parameters including sedation, blood pressure and adverse events, and the Physician Withdrawal Checklist; 20-item (PWC-20) will be administered (as applicable) to assess potential withdrawal symptoms after cessation of esketamine treatment.

Given the potential for treatment emergent transient elevation in systolic and diastolic blood pressure, heart rate and blood pressure will be monitored throughout the study and at multiple time points on dosing days. Specific guidance to be followed on intranasal dosing days is provided in Section 6.2.1.

Even though it is anticipated that the potential risk for treatment-emergent cystitis is very low based upon the doses to be used in this study, subjects will be monitored for symptoms of cystitis, bladder pain, and interstitial cystitis using the subject-completed Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) at specific time points.⁴⁰ A score >18 on the BPIC-SS scale is considered as probable cystitis, and any subjects that meet this cut-off will have a urinalysis and culture conducted at that visit to assess for potential urinary tract infection. Those without evidence of an ongoing urinary tract infection will be referred to a specialist for diagnostic workup. There are no definitive tests for diagnosing ulcerative cystitis. If a subject is determined to have a diagnosis of ulcerative cystitis, the subject must be discontinued from the study and followed up with appropriate medical care.

The effect of intranasal esketamine on cognition over the 4-week double-blind induction phase will be assessed using a computerized cognitive battery and Hopkins Verbal Learning Test-Revised (HVLT-R). The cognitive battery will provide assessment of multiple cognitive domains, including attention, visual learning and memory, and executive function. The HVLT-R is a measure of verbal learning and memory.

The University of Pennsylvania Smell Identification Test (UPSIT) will be performed to assess any treatment-emergent effects on the sense of smell.

On all intranasal dosing days, subjects must remain at the site until study procedures have been completed and the subject is ready for discharge. Subjects should be accompanied by a responsible adult when released from the clinical site. Subjects must not drive a car or work with machines for 24 hours after receiving intranasal study drug.

A list of prohibited medications is provided in [Attachment 1](#) as general guidance for the investigator (but is not all-inclusive).

3.2.7. Other Assessments

Patient Adherence Questionnaire

During the screening/prospective observational phase, the patient-reported Patient Adherence Questionnaire (PAQ) will be used to assess how often the subject has taken, and whether he or she has made any changes to, his or her antidepressant treatment regimen in the last 2 weeks. This assessment will provide confirmation of medication adherence when evaluating antidepressant treatment response. Subjects who report missing ≥ 4 days of antidepressant medication during a 2-week recall period will be discontinued because of inadequate adherence.

3.2.8. Pharmacokinetic Assessments

Pharmacokinetic samples will be obtained during the study for measurement of the plasma concentrations of esketamine, noreскетamine, and/or additional metabolites, if warranted.

3.2.9. Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations

Assessment of biomarkers (protein and RNA) and their potential relationship to the different treatment groups and to maintenance/stabilization of response, nonresponse, and relapse will be explored. Blood samples will be collected to measure genetic and epigenetic markers (including but not limited to BDNF allelic variants) and protein markers (including but not limited to growth factors, inflammation, endocrine, or metabolic). Samples of deoxyribonucleic acid (DNA) and biomarkers may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

Genetic variation can be an important contributory factor to inter-individual differences in drug distribution and response, and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain inter-individual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug or subgroups that are more susceptible to relapse. In addition, pharmacogenomics research may allow for the identification of genetic factors that influence the PK, PD, efficacy, safety, or tolerability of the different treatment groups, and for the identification of genetic factors associated with TRD or MDD. Specifically, genetic and epigenetic changes in genes known to be in pathways relevant to depression (eg, hypothalamic-pituitary-adrenal [HPA] axis, inflammation, growth factors, monoamine transporters, ion channels, and circadian rhythm, etc.) will be evaluated.

Protein, metabolite, and ribonucleic acid (RNA) biomarkers may aid in the elucidation of the mechanism of action of the different treatment groups or help to explain inter-individual variability in clinical outcomes or may help to identify population subgroups that respond differently to a drug or may help to identify subgroups that are more susceptible to relapse. The goal of the biomarker analyses is to evaluate the PD of the different treatment groups, and aid in evaluating the drug-clinical response relationship.

On the day of biomarker sample collection, it is recommended that subjects adhere to a low fat diet (as an alternative to fasting) to reduce the level of postprandial lipemia in blood samples because moderately or grossly lipemic specimens may interfere with assay results.

4. STUDY POPULATION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

4.1. Inclusion Criteria

1. Each potential subject must satisfy all of the following criteria to be enrolled in the study.
 - At the time of signing the informed consent form (ICF), subject must be a man or woman 65 years of age or older.
2. At the start of the screening/prospective observational phase, subject must meet the DSM-5 diagnostic criteria for single-episode MDD (if single episode MDD, the duration of episode must be ≥ 2 years) or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini International Neuropsychiatric Interview (MINI).
3. Criterion modified per Amendment 1
 - 3.1 Criterion modified per Amendment 2
 - 3.2 Criterion modified per Amendment 3
 - 3.3 At the start of the screening/prospective observational phase, subject must have had nonresponse ($\leq 25\%$ improvement) to ≥ 1 but ≤ 8 (if current episode is > 2 years, upper limit applicable to only the last 2 years) oral antidepressant treatments in the current episode of depression, assessed using the MGH-ATRQ and confirmed by documented records (eg, medical/pharmacy/prescription records, or a letter from the treating physician, etc.). In addition, subject is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose.
 - For specific tricyclic antidepressants which are ongoing and being taken at a dose below the MGH-ATRQ minimum therapeutic dose, a blood level that is within the therapeutic (antidepressant) range, is acceptable to establish the adequacy of the antidepressant treatment.
 - Subjects must be adherent to the continued oral antidepressant medication(s) (without adjustment in dosage) through the screening/prospective observational phase, as documented on the PAQ. Missing ≥ 4 days of antidepressant medication in the prior 2-week period will be considered as inadequate adherence.
 - Subjects who are nonresponders to the antidepressant medication(s) from the screening/prospective observational phase (as assessed by independent, remote raters) may be eligible for randomization if all other entry criteria are met. Non-response at the end of the screening/prospective observational phase is defined as $\leq 25\%$

- improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥ 24 on Week 2 and Week 4.
4. Criterion modified per Amendment 3
 - 4.1. At the start of the screening/prospective observational phase, subject must have an IDS-C30 total score of ≥ 31 .
 5. Criterion modified per Amendment 2
 - 5.1. Criterion modified per Amendment 3
 - 5.2. The subject's current major depressive episode, depression symptom severity (Week 1 MADRS total score ≥ 24 required), and antidepressant treatment response in the current depressive episode, must be confirmed using the Site Independent Qualification Assessment.
 6. Subject must be medically stable on the basis of physical examination, medical history, vital signs (including blood pressure), pulse oximetry, and 12-lead ECG performed in the screening/prospective observational phase. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, the determination of their clinical significance must be determined by the investigator and recorded in the subject's source documents and initialed by the investigator.
 7. Criterion modified per Amendment 1
 - 7.1 Criterion modified per Amendment 2
 - 7.2 Criterion modified per Amendment 3
 - 7.3 Subject must be medically stable on the basis of clinical laboratory tests performed in the screening/prospective observational phase. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator.
 - Subjects with a pre-existing history of thyroid disease/disorder who are treated with thyroid hormones must be on a stable dosage for 3 months prior to the start of the screening/prospective observational phase.
 - For any subject (regardless of thyroid history), if the thyroid stimulating hormone (TSH) value is out of range, a free thyroxine (fT4) will be conducted. If the fT4 value is abnormal and considered to be clinically significant (after discussion with the medical monitor), the subject is not eligible.
 8. Subject must be comfortable with self-administration of intranasal medication and be able to follow the intranasal administration instructions provided.

9. Criterion modified per Amendment 2

9.1. Criterion modified per Amendment 3

9.2 During the study (ie, from Day 1 of the double-blind induction phase, prior to randomization) and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of intranasal study medication, a man who is sexually active with a woman of childbearing potential

- must be practicing a highly effective method of contraception with his female partner from those listed above (see examples of highly effective methods of contraception provided for female subjects).
- must use a condom if his partner is pregnant.
- must agree not to donate sperm.

Note: If the female partner's childbearing potential changes after start of the study, the female partner of a male study subject must begin a highly effective method of birth control, as described above.

10. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

11. Each subject must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.

4.2. Exclusion Criteria

1. Criterion modified per Amendment 1

1.1. Criterion modified per Amendment 2

1.2. Any potential subject who meets any of the following criteria will be excluded from participating in the study.

The subject's depressive symptoms have previously demonstrated nonresponse to:

- Esketamine or ketamine in the current major depressive episode per clinical judgment, or
- All of the oral antidepressant treatment options available in the respective country for the double-blind induction phase (ie, duloxetine, escitalopram, sertraline, and venlafaxine XR) in the current major depressive episode (based on MGH-ATRQ), or
- An adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/bilateral ECT.

2. Criterion modified per Amendment 2

2.1. Subject who has received vagal nerve stimulation (VNS) or who has received deep brain stimulation (DBS) in the current episode of depression will be excluded.

3. Criterion modified per Amendment 1

3.1. Criterion modified per Amendment 2

3.2. Subject has a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features, bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current episode only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder.

4. Subject has homicidal ideation/intent, per the investigator's clinical judgment, or has suicidal ideation with some intent to act within 6 months prior to the start of the screening/prospective observational phase, per the investigator's clinical judgment or based on the Columbia Suicide Severity Rating Scale (C-SSRS), corresponding to a response of "Yes" on Item 4 (active suicidal ideation with some intent to act, without specific plan) or 5 (active suicidal ideation with specific plan and intent) for suicidal ideation on the C-SSRS, or a history of suicidal behavior within the past year prior to start of the screening/prospective observational phase. Subjects reporting suicidal ideation with intent to act or suicidal behavior prior to the start of the double-blind induction phase should be excluded.
5. Subject has a history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria, except nicotine or caffeine, within 6 months before the start of the screening/prospective observational phase.
 - A history (lifetime) of ketamine, phencyclidine (PCP), lysergic acid diethylamide (LSD), or 3, 4-methylenedioxy-methamphetamine (MDMA) hallucinogen-related use disorder
6. Subjects with a current or past history of seizures (uncomplicated childhood febrile seizures with no sequelae are not exclusionary)
7. Criterion deleted per Amendment 3
8. Criterion modified per Amendment 2

8.1. Subject has one of the following cardiovascular-related conditions:

- Cerebrovascular disease with a history of stroke or transient ischemic attack.
- Aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels).
- Coronary artery disease with myocardial infarction, unstable angina, or revascularization procedure (eg, coronary angioplasty or bypass graft surgery) within 12 months before the start of the screening/prospective observational phase. Subjects who have had a revascularization performed >12 months prior to screening and are clinically stable and symptom-free, per investigator's clinical judgment, can be included.
- Hemodynamically significant valvular heart disease such as mitral regurgitation, aortic stenosis, or aortic regurgitation.

- New York Heart Association (NYHA) Class III-IV heart failure of any etiology (refer to [Attachment 2](#)).

9. Criterion modified per Amendment 2

9.1. Subject has a history of uncontrolled hypertension despite diet, exercise, or antihypertensive therapy at the start of the screening/prospective observational phase or any past history of hypertensive crisis or ongoing evidence of uncontrolled hypertension defined as a supine systolic blood pressure (SBP) >150 mm Hg or diastolic blood pressure (DBP) >90 mm Hg during screening/prospective observational phase which continues to be above this range with repeated testing during this phase. Note: On Day 1 of the double-blind induction phase prior to randomization a supine SBP >150 mm Hg or DBP >90 mm Hg is exclusionary.

- A potential subject may have his/her current antihypertensive medication(s) adjusted during the screening/prospective observational phase and be re-evaluated to assess their blood pressure control. The subject must be on a stable regimen for at least 2 weeks before Day 1 of the double-blind induction phase.

10. Subject has a current or past history of significant pulmonary insufficiency/condition or with an arterial blood oxygen saturation of <93% at the start of the screening/prospective observational phase or Day 1 prior to randomization will be excluded.

11. Criterion modified per Amendment 3.

11.1. Subject has a Mini Mental State Examination (MMSE) <25 or <22 for those subjects with less than an equivalent of high school education.

12. Criterion modified per Amendment 3.

12.1. Subject has neurodegenerative disorder (eg, Alzheimer's Disease, Vascular dementia, Parkinson's disease with clinical evidence of cognitive impairment) or evidence of mild cognitive impairment (MCI).

13. Criterion modified per Amendment 2

13.1. Criterion modified per Amendment 3

13.2. Subject has clinically significant ECG abnormalities at the start of the screening/prospective observational phase or on Day 1 of the double-blind induction phase prior to randomization, defined as:

- During screening a QT interval corrected according to Fridericia's formula (QTcF): ≥ 450 msec; if the QTcF is prolonged on the initial ECG, the average QTcF of three ECGs, recorded at least 4 minutes apart must not be ≥ 450 msec.

- On Day 1 (predose), a QT interval corrected according to Fridericia's formula (QTcF): ≥ 450 msec based on the site-evaluated ECG; if the QTcF is prolonged on the initial ECG, the average QTcF of three ECGs, recorded at least 4 minutes apart, must not be ≥ 450 msec.
- Evidence of 2nd and 3rd degree AV block, or, complete left bundle branch block (LBBB), or complete right bundle branch block (RBBB).
- Features of new ischemia.
- Arrhythmia (except premature atrial contractions [PACs] and premature ventricular contractions [PVCs]).

14. Criterion modified per Amendment 2

14.1 Subject has a history of additional risk factors for Torsades des Pointes (eg, heart failure, hypokalemia, family history of Long QT Syndrome).

15. Criterion modified per Amendment 2

15.1 Subject has history of, or symptoms and signs suggestive of, liver cirrhosis (eg, esophageal varices, ascites, and increased prothrombin time) OR alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values ≥ 2 times the upper limit of normal or total bilirubin > 1.5 times the ULN in the screening/prospective observational phase.

- Repeat of the screening test for abnormal ALT and AST is permitted once during the screening period, per investigator discretion, provided there is an explanation for a transient out of range value.
- For elevations in bilirubin if, in the opinion of the investigator and agreed upon by the sponsor's medical officer, the elevation in bilirubin is consistent with Gilbert's disease, the subject may participate in the study.

16. Criterion modified per Amendment 2

16.1. Criterion modified per Amendment 3

16.2 Subject has positive test result(s) for drugs of abuse (including barbiturates, methadone, opiates, cocaine, phencyclidine, and amphetamine/methamphetamine) at the start of the screening/prospective observational phase or Day 1 of the double-blind induction phase prior to randomization.

- Subjects who have a positive test result at screening due to prescribed psychostimulants (eg, amphetamine, methylphenidate, etc.) taken for an indication other than MDD are permitted to continue to take this medication during the study in accordance with Attachment 1.

- Otherwise, subjects who have a positive test result at screening due to prescribed/over-the-counter opiates, or barbiturates may be permitted to continue in the screening/prospective observational phase if the medication is discontinued at least 1 week or 5 half-lives, whichever is longer, before Day 1 of the double-blind induction phase (prior to randomization) (for barbiturates or amphetamines/methamphetamine) or used in accordance with [Attachment 1](#) restrictions (for opiates). The result of the Day 1 (prior to randomization) test for drugs of abuse must be negative for the subject to be randomized.
 - Retesting is not permitted for positive test result(s), except for reasons stated above.
 - Prior intermittent use of cannabinoids prior to the start of the screening/prospective observational phase is not exclusionary as long as the subject does not meet the criteria for substance use disorder. Although tested at screening, a positive test for cannabinoids at the start of the screening/prospective phase is not exclusionary; however, a positive test result for cannabinoids predose on Day 1 of the double-blind induction phase is exclusionary.
17. Subjects who are taking a total daily dose of benzodiazepines greater than the equivalent of 6 mg/day of lorazepam at the start of the screening/prospective observational phase.
18. Criterion modified per Amendment 2
- 18.1. Subject has uncontrolled diabetes mellitus, as evidenced by HbA1c >9% in the screening/prospective observational phase or history in the prior 3 months prior to the start of the screening/prospective observational phase of diabetic ketoacidosis, hyperglycemic coma, or severe hypoglycemia with loss of consciousness.
19. Subject has untreated glaucoma, current penetrating or perforating eye injury, brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure or increased intraocular pressure or planned eye surgery.
20. Criterion modified per Amendment 2
- 20.1. Subject has any anatomical or medical condition that, per the investigator's clinical judgment based on assessment, may impede delivery or absorption of the intranasal study drug.
21. Criterion deleted per Amendment 2
22. Subject has a history of malignancy within 5 years before the start of the screening/prospective observational phase (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that, in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).

23. Subject has known allergies, hypersensitivity, intolerance, or contraindications to esketamine/ketamine and/or its excipients or all of the available oral antidepressant treatment options for the double-blind induction phase.
24. Subject has taken any prohibited therapies that would not permit dosing on Day 1, as noted in Section 8 (Prestudy and Concomitant Therapy) and [Attachment 1](#).
25. Criterion modified per Amendment 2
- 25.1 Subject has a score of ≥ 5 on the STOP-Bang questionnaire, in which case obstructive sleep apnea must be ruled out (eg, apnea-hypopnea index [AHI] < 30). A subject with obstructive sleep apnea can be included if he or she is using a positive airway pressure device or other treatment/therapy that is effectively treating (ie, AHI < 30) his or her sleep apnea.
26. Criterion modified per Amendment 2
- 26.1 Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 60 days before the start of the screening/prospective observational phase, or has participated in 2 or more MDD or other psychiatric condition clinical interventional studies (with different investigational drugs including investigational vaccines or investigational medical devices for each study) in the previous 1 year before the start of the screening/prospective observational phase, or is currently enrolled in an investigational interventional study.
27. Subject has a diagnosis of acquired immunodeficiency syndrome (AIDS). Human immunodeficiency virus (HIV) testing is not required for this study.
28. Subject has any condition or situation/circumstance for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
29. Subject has had major surgery, (eg, requiring general anesthesia) within 12 weeks before the start of the screening/prospective observational phase, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study.
- Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.
30. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.
31. Subject has severe renal impairment (creatinine clearance < 30 ml/min).

NOTE: Investigators should ensure that all study enrollment criteria have been met. If a subject's status changes (including laboratory results or receipt of additional medical records)

before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

The sponsor will evaluate and approve/reject requests to rescreen an individual subject on a case-by-case basis.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

- Refer to Section 4.1, Inclusion Criteria for information regarding contraception requirements for males who are sexually active with a woman of childbearing potential.
- Refer to Section 8 (Prestudy and Concomitant Therapy) and Attachment 1 (Prohibited Concomitant Medications for Intranasal Study Medication [Esketamine or Placebo]) for further information on prohibited therapies.
- Subjects taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening/prospective observational phase can continue these medications during the induction phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the induction phase, with the exception of the use of permitted benzodiazepine rescue medication. Benzodiazepines and non-benzodiazepine sleeping medication (eg, zolpidem, zaleplon, eszopiclone, and ramelteon) are prohibited within 12 hours prior to the start of each intranasal treatment session or cognition testing.
- A positive urine drug screen after Day 1 for use of PCP or cocaine from Day 1 of the induction phase through the final visit in the double-blind induction phase will lead to discontinuation.
- Subjects must abstain from using alcohol within 24 hours before and after each intranasal treatment session. If a subject appears intoxicated, dosing should not occur (delayed per the permitted visit window; see the Time and Events Schedule).
- On all intranasal study drug dosing days, all subjects must remain at the clinical study site until study procedures have been completed and the subject is ready for discharge. Subjects should be accompanied by a responsible adult when released from the clinical study site. Subjects must not drive a car or work with machines for 24 hours after study drug dosing.
- ECT, DBS, transcranial magnetic stimulation (TMS), and VNS are prohibited from study entry through the end of the double-blind induction phase.
- Subjects receiving psychotherapy (including cognitive behavioral therapy; CBT) can continue receiving psychotherapy; however, CBT must have been ongoing for the last 3 months prior to the screening/prospective observational phase. With the exception of new CBT, which is prohibited, new psychotherapy is allowed during this study. Any change in existing therapy or new therapy must be documented on the concomitant therapies form.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation and Randomization

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by country and class of oral antidepressant (SNRI or SSRI) to be initiated in the double-blind induction phase. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kits for the subject. After the investigator selects the oral antidepressant treatment for the double-blind induction phase, the site will enter this information into IWRS. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (eg, intranasal study drug plasma concentrations, treatment allocation) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee, if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and time of the unblinding will be documented by the IWRS, and reason for the unblinding must be documented in the electronic CRF (eCRF) and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded should continue to return for scheduled early withdrawal and follow-up visits.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. For interim analysis, the randomization codes and, if required, the

translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim analysis.

To maintain the blinding of intranasal study medication, the esketamine and placebo intranasal devices will be indistinguishable. Please refer to Section 14 (Study Drug Information) for information on the physical characteristics of the study drugs and devices. In order to manage clinical supplies, the clinical supplies group will be informed of the decision made at interim analysis so that only the required amount of study medication will be packaged.

6. DOSAGE AND ADMINISTRATION

6.1. Screening/Prospective Observational Phase

As described in Section 9.1.2, at the start of screening/prospective observational phase, the subject must have had documented nonresponse to at least one antidepressant treatment (based on MGH-ATRQ criteria) in the current episode of depression, and the subject is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other ongoing medications being taken for depression at screening (including adjunctive/augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4.

Non-response at the end of the screening/prospective observational phase is defined as $\leq 25\%$ improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥ 24 on Week 2 and Week 4.

The sponsor will not supply these antidepressant medication(s).

During this phase, antidepressant treatment adherence will be assessed using the PAQ.

After the completion of 4 weeks of prospective antidepressant treatment and assessment of the antidepressant treatment response, eligible subjects will have all antidepressant medication(s), including adjunctive/augmentation therapies discontinued. Of note, subjects taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening/prospective observational phase can continue these medications. No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the screening/prospective observational phase. If clinically indicated, the antidepressant treatment(s) may be tapered and discontinued over a period of up to 3 weeks per the local prescribing information or clinical judgment (eg, antidepressants with short half-lives, such as venlafaxine XR). Eligible subjects who do not require a tapered discontinuation of their antidepressant treatment(s) can immediately proceed into the double-blind induction phase.

6.2. Double-Blind Induction Phase

During this phase subjects will self-administer double-blind intranasal treatment with flexibly dosed intranasal esketamine (28 mg, 56 mg or 84 mg) or placebo twice per week for 4 weeks as a flexible dose regimen at the study site. In addition, subjects will simultaneously initiate a new, open-label oral antidepressant (ie, duloxetine, escitalopram, sertraline, or venlafaxine XR) on Day 1 that will be continued for the duration of this phase.

Intranasal Study Drug

On all intranasal treatment session days, a site staff member with training in cardiopulmonary resuscitation (eg, Basic Life Support course or equivalent courses) that is up to date per local regulations must be present with the subject during the intranasal treatment sessions and the postdose observation period. In addition, equipment for supportive ventilation and resuscitation needs to be present.

Table 3 describes how each intranasal treatment session will be administered in the double-blind induction phase. Please refer to Section 6.2.1 for guidance on blood pressure monitoring on intranasal dosing days.

Table 3: Intranasal Treatment Sessions Administration During the Double-blind Induction Phase

Intranasal Treatment	Time of Intranasal Device Administration		
	0 ^a	5 minutes	10 minutes
Intranasal Device ^b	1 st	2 nd	3 rd
Placebo for 28 mg	1 spray of placebo to each nostril	Not applicable	Not applicable
Esketamine 28 mg	1 spray of esketamine to each nostril	Not applicable	Not applicable
Placebo for 56 mg	1 spray of placebo to each nostril	1 spray of placebo to each nostril	Not applicable
Esketamine 56 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	Not applicable
Placebo for 84 mg	1 spray of placebo to each nostril	1 spray of placebo to each nostril	1 spray of placebo to each nostril
Esketamine 84 mg	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril	1 spray of esketamine to each nostril

^a Time 0 is defined as the time of administration of the first intranasal spray to one nostril from the first intranasal device.

^b One device will be used at each time point. Each individual intranasal device contains 2 sprays. The intranasal devices containing esketamine deliver 14 mg per spray, for a total of 28 mg per individual device (ie, 2 sprays).

Instructions for use documents (subject and healthcare provider versions) for intranasal study drug administration will be provided as separate documents. Details regarding study drug administration will be recorded in the source documents and the eCRF.

All subjects will self-administer the intranasal study drug (esketamine or placebo) at treatment sessions twice a week for 4 weeks at the study site. The first treatment session will be on Day 1. Intranasal treatment sessions should not take place on consecutive days.

- Prior to the first intranasal dose on Day 1, subjects will practice spraying (into the air, not intranasally) a demonstration intranasal device that is filled with a placebo solution.

- Instructions for intranasal dosing:
 - After Day 1 (28 mg), all dosing decisions are to be determined by the investigator based on efficacy and tolerability.
 - Prior to intranasal dosing, subjects must not have a blood pressure >150 mm Hg systolic and/or >90 mm Hg diastolic.
 - Prior to any dose escalation, subjects must have had a postdose blood pressure, on the prior intranasal dosing day, of <180 mm Hg for systolic and <100 mm Hg for diastolic blood pressure.
- Dose titration of intranasal esketamine will be performed as outlined in [Table 4](#):

Table 4 Dose Titration of Intranasal Esketamine*

Day	Dose	Dose Titration Guidance
Day 1	28 mg	
Day 4	28 or 56 mg	The dose may remain at 28mg or be increased to 56mg , as determined by the investigator based on efficacy and tolerability
Days 8, 11, 15	28, 56 or 84 mg	The dose may be maintained, or increased or reduced by 28mg from the previous dosing session, as determined by the investigator based on efficacy and tolerability. No dose increase is permitted beyond Day 15.
Days 18, 22 and 25	28, 56 or 84 mg	No dose increase is permitted beyond Day 15. If needed for tolerability, dose reduction by 28mg from the previous dose is permitted on Days 18, 22 and 25.

* Dose changes are determined by the investigator based on efficacy and tolerability and in accordance with blood pressure guidelines.

From Day 8 to Day 15, inclusive, for those who have had a prior down titration from a higher dose, a dose increase by 28 mg is allowed based on clinical judgment.

Food will be restricted for at least 2 hours before each administration of study drug. Drinking of any fluids will be restricted for at least 30 minutes before the first nasal spray.

If the subject has nasal congestion on the dosing day an intranasal decongestant may be used to reduce congestion. Subjects should wait for at least 1 hour after using an intranasal decongestant before administering intranasal study drug.

For all intranasal treatment sessions, subjects must remain at the clinical site until study procedures have been completed and the subject is ready for discharge, and should be accompanied by a responsible adult when released from the clinical study site. Subjects must not drive a car or work with machines for 24 hours after intranasal treatment sessions.

Oral Antidepressant Medication

Starting on Day 1, a new, open-label oral antidepressant treatment will be initiated in all subjects, and continued for the duration of this phase. The oral antidepressant will be 1 of 4 oral antidepressant medications (duloxetine, escitalopram, sertraline, or venlafaxine XR). The antidepressant medication will be assigned by the investigator based on review of the

MGH-ATRQ and relevant information regarding prior antidepressant treatments, and will be one that the subject has not previously had a nonresponse to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country.

Dosing of the oral antidepressant will begin on Day 1. A mandatory titration schedule is provided in [Attachment 3](#). Doses are not to exceed the maximum dose defined in the titration schedule. As patients may not be able to tolerate the higher doses of the oral antidepressant during the induction phase, a down titration of the dose is permitted based on clinician's judgment.

All subjects entering the follow-up phase will be provided with an additional 2-week supply of the oral antidepressant medication following the double-blind induction phase, to ensure there is no interruption of antidepressant therapy during the transition to further clinical/standard of care in the follow-up phase.

Study-site personnel will instruct subjects on how to take/use and store the oral antidepressants supplied during this study for at-home use as indicated in this protocol. A subject diary to capture oral antidepressant study medication use will be provided.

On intranasal dosing days, it is recommended that the oral antidepressant medication not be taken until at least 3 hours after an intranasal treatment session.

6.2.1. Guidance for Blood Pressure Monitoring on Intranasal Treatment Session Days

Given the potential for treatment emergent transient elevation in systolic and diastolic blood pressure, the following guidance should be followed on intranasal dosing days:

- If subsequent to fulfilling the inclusion and exclusion criteria on Day 1 (ie, applicable for all other intranasal treatment session days after Day 1), a subject's predose SBP is >150 mmHg and/or DBP is >90 mmHg, it is recommended that the blood pressure measurement is repeated after the subject rests in sitting or recumbent position. If after rest and repeated measurements, the predose SBP is >150 mmHg and/or the DBP is >90 mmHg, then dosing should be postponed and the subject scheduled to return on the following day or within the given visit window. If the blood pressure elevation still persists on the next visit, the subject will be scheduled for a consultation by cardiologist, other specialist, or a primary care physician prior to further dosing.
- If at any postdose time point on the dosing day the SBP is ≥ 180 mm Hg but <190 mm Hg and/or the DBP is ≥ 100 mm Hg but <110 mm Hg, further intranasal dosing should be interrupted and the subject should be referred to a cardiologist, other specialist, or primary care physician for a follow-up assessment.
 - After the assessment by a cardiologist, other specialist, or primary care physician, if recommended by the referring doctor and considered appropriate according to the clinical judgment of the investigator for the subject to continue in the study, the subject may continue with intranasal dosing if the pre-dose blood pressure at the next scheduled visit is within the acceptable range (see bullet above).

- If at any postdose time point on a dosing day the SBP is ≥ 190 mm Hg and/or the DBP is ≥ 110 mm Hg, the subject must discontinue from further dosing and be referred to a cardiologist, other specialist, or primary care physician for a follow-up assessment.
- During the double-blind induction phase, at 1.5 hours postdose, if the SBP is ≥ 160 mm Hg and/or the DBP ≥ 100 mm Hg, assessments should continue every 30 minutes until:
 - the blood pressure is < 160 mm Hg SBP and < 100 mm Hg DBP, or
 - in the investigator's clinical judgment, the subject is clinically stable and can be discharged from the study site, or
 - the subject is referred for appropriate medical care if clinically indicated.

If the blood pressure remains ≥ 180 SBP and/or ≥ 110 mmHg DBP 2 hours after dosing, the subject should be referred for immediate medical treatment.

6.3. Follow-up Phase

Subjects who receive at least 1 dose of intranasal study medication in the double-blind induction phase, but do not enter the subsequent ESKETINTRD3004 safety study, will proceed into the 2-week follow-up phase. A 2-week supply of oral antidepressant will be provided for subjects entering the follow-up phase.

No intranasal study medication will be administered during this phase.

At the start of the follow-up phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the subject's treating physician. All subjects will be provided with an additional 2-week supply of the oral antidepressant medication to ensure there is no interruption of antidepressant therapy during the transition to further clinical/standard of care.

The decision to continue the oral antidepressant medication in this phase will be at the discretion of the investigator; however, in order to better assess potential withdrawal symptoms from the intranasal study medication and facilitate maintenance of clinical benefit following the 4-week double blind treatment phase, the oral antidepressant medication should be continued for the 2 weeks of the follow-up phase unless determined as not clinically appropriate.

7. TREATMENT COMPLIANCE

The investigator or designated study-site personnel will maintain a log of all intranasal study drug and oral antidepressant medication dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study.

Subjects will receive instructions on compliance with the oral antidepressant treatment. During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to re-educate any subject to ensure compliance with taking the oral antidepressant. A subject diary will be provided to capture oral antidepressant study medication use.

Antidepressant treatment adherence during the screening/prospective observational phase will be assessed using the PAQ. Missing ≥ 4 days of antidepressant medication in the prior 2-week period will be considered inadequate compliance.

Antidepressant treatment adherence during the double-blind induction and follow-up phases will be assessed by performing pill counts (ie, compliance check) and drug accountability.

All doses of intranasal study drug will be self-administered by the subjects at the investigative site under the direct supervision of the investigator or designee, and will be recorded.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy non-antidepressant therapies administered up to 30 days before the start of the screening/prospective observational phase must be recorded at the start of this phase.

All antidepressant treatment(s), including adjunctive treatment for MDD, taken during the current depressive episode (ie, including those taken more than 30 days prior to the start of the screening/prospective observational phase) will be recorded at the start of the screening/prospective observational phase. In addition, information will also be obtained regarding any history of intolerance to any of the 4 antidepressant choices (ie, duloxetine, escitalopram, sertraline, and venlafaxine XR). Antidepressant treatments which are not listed on the MGH-ATRQ but were used or are currently being used as antidepressant treatment in the current depressive episode must be recorded on the 'Concomitant Therapy' eCRF.

Any medication that is listed on the MGH-ATRQ and is being taken at the start of the screening/prospective observational phase for an indication other than depression (eg, insomnia) should be continued during the screening/prospective observational phase but must be discontinued before the start of the double-blind phase.

Concomitant therapies must be recorded throughout the study, beginning with signing of the informed consent and continuing up to the last visit. Information on concomitant therapies should also be obtained beyond this time only in conjunction with new or worsening adverse events until resolution of the event.

Subjects should continue to take their permitted concomitant medications (eg, antihypertensive medications) at their regular schedule, taking into account any restrictions as outlined in Section 4.3 and [Attachment 1](#). Of note, if a subject has routinely taken his/her oral antihypertensive medications in the morning, the morning dose should be taken prior to intranasal dosing.

Subjects receiving psychotherapy (including cognitive behavioral therapy; CBT) can continue receiving psychotherapy; however, CBT must have been ongoing for the last 3 months prior to the start of the screening/prospective observational phase. With the exception of new CBT, which is prohibited, new psychotherapy is allowed during the study. Any change in existing therapy or new therapy must be documented on the concomitant therapies form.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; nonpharmacologic therapies such as psychotherapy, electrical stimulation [eg, VNS or DBS], acupuncture, special diets, and exercise regimens, cognitive behavioral therapy) different from the study drug must be recorded in the eCRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study, unless permitted by protocol (eg, adjustment of blood pressure medications).

Rescue Medications

Rescue medications will not be supplied by the sponsor. In case of treatment-emergent adverse events that cannot be resolved by stopping further administration of intranasal esketamine/placebo, the following rescue medications may be considered:

- For agitation or anxiety: As required, midazolam (maximum dose 2.5 mg orally or IM) or short acting benzodiazepine
- For nausea: As required, ondansetron 8 mg sublingually, metoclopramide (10 mg orally or IV or IM) or dimenhydrinate (25 to 50 mg, IV or IM)
- Unless clinically indicated, it is recommended that transient increases in blood pressure not be treated, as the blood pressure typically returns to predose values in 2 hours. The effect of any treatment may result in hypotension.

Prohibited Medications

A list of prohibited medications is provided in [Attachment 1](#) as general guidance for the investigator (but is not all inclusive).

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, PK, biomarker, pharmacogenomic, health economic, and safety measurements applicable to this study.

With the exception of postdose assessments, visit-specific patient-reported outcomes (PRO) assessments should be conducted or completed before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions. A recommended order of study procedures will be provided to the sites as a separate document.

Actual dates and times of assessments will be recorded in the source documentation and eCRF.

The approximate total blood volume to be collected from each subject will be approximately 112.0 mL ([Table 5](#)). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 5: Volume of Blood to Be Collected From Each Subject

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Total Volume of Blood (mL) ^a
Screening/Prospective Observational Phase			
Serum chemistry ^b	5	1	5
TSH	3.5	1	3.5
Hematology ^c	2	1	2
Biomarker: protein	10	1	10
Biomarker: DNA	6	1	6
Biomarker: RNA	2.5	1	2.5
Tricyclic Antidepressant Blood level ^d	6	1	6
fT4 ^e	3.5	1	3.5
Double-blind Induction Phase			
Serum chemistry	2.5	2	5
Hematology	2	2	4
Pharmacokinetic	2	2	4
Biomarker: protein (at Visits 2.1, 2.3, and 2.8)	10	3	30
Biomarker: DNA	6	1	6
Biomarker: RNA	2.5	3	7.5
Follow-up Phase			
Serum chemistry	2.5	1	2.5
Hematology	2	1	2
Biomarker: protein	10	1	10
Biomarker: RNA	2.5	1	2.5
Approximate volume of blood collected during the study			112.0 mL

Abbreviations: DNA, deoxyribonucleic acid; fT4, free thyroxine; RNA, ribonucleic acid; TSH, thyroid-stimulating hormone.

^a Calculated as number of samples multiplied by amount of blood per sample.

^b Serum chemistry includes lipid panel.

^c As needed, HbA1c will be measured from the sample collected for hematology.

^d For specific tricyclic antidepressants which are being taken at a dose below the MGH-ATRQ minimum therapeutic dose, a blood level that is within the therapeutic (antidepressant) range, is acceptable to establish the adequacy of the antidepressant treatment.

^e For any subject (regardless of thyroid history), if the TSH value is out of range, a free thyroxine (fT4) will be conducted.

Note: An indwelling IV cannula may be used for blood sample collection.

Note: Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

9.1.2. Screening/Prospective Observational Phase

Prior to conducting any study procedure, the investigator (or designated study personnel) will review and explain the written ICF to each subject. After signing the ICF, subjects who are 65 years of age and older, will be screened to determine eligibility for study participation (please refer to the study entry criteria listed in Section 4).

Subjects must meet DSM-5 diagnostic criteria for single episode MDD (if single episode MDD, duration of episode must be ≥ 2 years) or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the MINI. Subjects must also have a mini mental state examination (MMSE) total score of < 25 . In addition, at the start of the screening/prospective observational phase, the subject must have an IDS-C₃₀ total score ≥ 31 .

At the start of this phase, subjects must have had nonresponse ($\leq 25\%$ improvement) to ≥ 1 but ≤ 8 (if current episode is > 2 years, upper limit applicable to only the last 2 years) different oral antidepressant treatments taken at adequate dosage and for adequate duration, as assessed using

the MGH-ATRQ and documented by records (eg, medical/pharmacy/prescription records or a letter from treating physician, etc.) for the current episode of depression.

At the start of the screening/prospective observational phase, the subject must have had documented nonresponse to at least one antidepressant treatment (based on the MGH-ATRQ criteria) in the current episode of depression, and the subject is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose. This antidepressant treatment, as well as any other ongoing medications being taken for depression at screening (including adjunctive/augmentation therapies), will continue from the start of Week 1 through the end of Week 4 of the screening/prospective observational phase. Dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4.

Antidepressant treatment adherence will be assessed using the PAQ. Missing ≥ 4 days of antidepressant medication in the prior 2-week period will be considered as inadequate adherence.

The subject's current major depressive episode, depression symptom severity (Week 1 MADRS total score ≥ 24 required) and antidepressant treatment response to antidepressant therapies used during the current depressive episode will be confirmed using the Site Independent Qualification Assessment.

An independent, blinded rater will perform remote MADRS assessments to assess depressive symptoms during this phase.

After 4 weeks, subjects who are nonresponders to the current oral antidepressant treatment may be eligible to proceed to the double-blind induction phase. Non-response at the end of the screening/prospective observational phase is defined as $\leq 25\%$ improvement in the MADRS total score from Week 1 to Week 4 and a MADRS total score of ≥ 24 on Week 2 and Week 4. Eligible subjects who are entering the double-blind induction phase will discontinue all of their current medication(s) being used for depression treatment, including adjunctive/augmentation therapies and any other prohibited psychotropic medications, including adjunctive atypical antipsychotics. Subjects who are taking benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day of lorazepam) and/or permitted nonbenzodiazepine sleep medications (eg, zolpidem, zaleplon) during the screening/prospective observational phase can continue these medications during the induction phase. No dose increases beyond the equivalent of 6 mg/day of lorazepam or new benzodiazepine medications are permitted during the induction phase, with the exception of the use of permitted benzodiazepine rescue medication. Benzodiazepines and non-benzodiazepine sleeping medications (eg, zolpidem, zaleplon, eszopiclone, and ramelteon) are prohibited within 12 hours prior to the start of each intranasal treatment session or cognition testing.

All other subjects who do not proceed to the double-blind induction phase will end study participation at this time. No further study visits or follow-up is required.

Optional Antidepressant Taper Period

Since all nonresponder subjects will be starting a new oral antidepressant during the double-blind induction phase, no washout or drug-free period is required after discontinuing the current antidepressant treatment. However, an additional, optional period of up to 3 weeks is permitted to taper and discontinue the current oral antidepressant medication per the local prescribing information or clinical judgment.

If clinically indicated, a subject's current antidepressant treatment(s) may be tapered and discontinued over an additional optional period of up to 3 weeks, per the local prescribing information or per clinical judgment. This 3 week period may also be used to optimize medical management if needed to facilitate subject participation (eg, treatment of blood pressure or diabetes, wean from other medications, etc.). In such cases, if there is no planned taper, the oral regimen should be continued in the interim and then discontinued by Day 1 of the double-blind induction phase.

The taper period should not begin until after the completion of 4 weeks of prospective antidepressant treatment and assessment of the antidepressant treatment response.

9.1.3. Double-Blind Induction Phase

During this phase, subjects will self-administer double-blind intranasal treatment with flexibly-dosed intranasal esketamine (28 mg, 56 mg or 84 mg) or placebo twice per week for 4 weeks as a flexible dose regimen. In addition, subjects will simultaneously initiate a new, open-label oral antidepressant (please refer to Section 6, Dosage and Administration).

On Day 1, approximately 148 eligible subjects with TRD will be randomly assigned to 1 of the following 2 double-blind treatment groups, in a 1:1 ratio (approximately 74 subjects per group):

- Intranasal placebo
- Intranasal esketamine

On the same day (ie, Day 1), subjects will be switched to a new, open-label oral antidepressant treatment. The oral antidepressant will be 1 of 4 oral antidepressant medications (duloxetine, escitalopram, sertraline, or venlafaxine XR). The selection of the antidepressant medication assigned by the investigator (based on review of the MGH-ATRQ and relevant prior antidepressant treatment information) and will be one that the subject has not previously had a nonresponse to in the current depressive episode, has not been previously intolerant to (lifetime), and is available in the participating country. Dosing of the oral antidepressant will begin on Day 1. A mandatory titration schedule is provided in [Attachment 3](#). Doses are not to exceed the maximum dose defined in the titration schedule. A dose reduction for tolerability is permitted.

For information obtained via telephone contact, written documentation of the communication must be available for review in the source documents. During telephone contact visits with the subject by site personnel, adverse event and concomitant therapy information will be obtained. In addition, specified clinician-administered assessments (eg, PWC-20) will be performed by appropriately qualified staff.

At the end of the double-blind induction phase, subjects may be eligible to enter the subsequent long term safety study (Study ESKETINTRD3004). Subjects who do not complete the induction phase of this study will not be eligible to participate in the ESKETINTRD3004 study. To maintain study blinding, the blind will not be broken for subjects entering Study ESKETINTRD3004. Participation in ESKETINTRD3004 will begin immediately after the completion of the double-blind induction phase. These subjects will be instructed to continue taking their oral antidepressant medication through their next study visit (ie, first study visit Study ESKETINTRD3004).

Those subjects who do not enter Study ESKETINTRD3004 will proceed into a 2-week follow-up phase.

Early Withdrawal

If a subject withdraws before the end of the double-blind induction phase for reasons other than withdrawal of consent, the Early Withdrawal visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase. If the Early Withdrawal visit occurs on the same day as a scheduled visit, the early withdrawal visit can be performed on the same day and duplicate assessments are not required.

Further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the subject's treating physician. The study investigator and/or treating physician will determine whether or not the current oral antidepressant medication will continue.

Subjects who withdraw early will receive additional oral antidepressant medication, if applicable, and they should continue taking the oral antidepressant medication for the 2 weeks of the follow-up phase, unless determined as not clinically appropriate.

9.1.4. Follow-up Phase

All subjects who receive at least 1 dose of intranasal study medication in the double-blind induction phase and are not participating in the subsequent ESKETINTRD3004 study will proceed into the 2-week follow-up phase. Clinic visits and remote assessment visits will be performed as specified in the Time and Events Schedule. During this phase, safety and tolerability, including potential withdrawal symptoms, following discontinuation of intranasal esketamine will be assessed. In order to better assess potential withdrawal symptoms from the intranasal medication it is recommended that the oral antidepressant medication be continued in the follow-up phase unless determined as not clinically appropriate.

Further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the subject's treating physician. No intranasal study medication will be administered during this phase. All subjects will be provided with an additional 2-week supply of their oral antidepressant medication, to ensure there is no interruption of antidepressant therapy during the transition to further clinical/standard of care. In order to better assess potential withdrawal symptoms from the intranasal medication and facilitate maintenance of clinical benefit following the 4-week double blind treatment phase, the oral antidepressant medication

should be continued for the 2 weeks of the follow-up phase unless determined as not clinically appropriate. The decision to continue the antidepressant will be at the discretion of the investigator.

If information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents.

Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached. All adverse events and special reporting situations, whether serious or non-serious, will be reported until completion of the subject's last study-related procedure.

9.2. Efficacy

9.2.1. Evaluations

It is recommended that the patient-reported outcome assessments be completed prior to other procedures.

9.2.1.1. Primary Efficacy Evaluation

The primary efficacy evaluation will be the change from baseline in the MADRS total score from Day 1 pre-randomization to the end of the 4-week double-blind induction phase. The structured interview guide for the MADRS (SIGMA) will be used for each administration. The MADRS will be performed by independent remote raters during the study.

The MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment.⁴⁹ The scale consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability.

The typical recall period for the MADRS is 7 days and will be used for the primary efficacy evaluation.

9.2.1.2. Secondary Efficacy Evaluations (Clinician-completed)

9.2.1.2.1. CGI-S

The CGI-S provides an overall clinician-determined summary measure of the severity of the subject's illness that takes into account all available information, including knowledge of the subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the subject's ability to function.³⁵ The CGI-S evaluates the severity of psychopathology on a scale of 0 to 7. Considering total clinical experience, a subject is assessed on severity of mental illness at the time of rating according to: 0=not assessed; 1=normal (not at all ill); 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill;

7=among the most extremely ill patients. The CGI-S permits a global evaluation of the subject's condition at a given time.

9.2.1.3. Other Secondary Efficacy Evaluations (Patient-reported Outcomes)

9.2.1.3.1. EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome, primarily designed for self-completion by respondents. It consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of the 5 dimensions is divided into 5 levels of perceived problems (Level 1 indicating no problem, Level 2 indicating slight problems, Level 3 indicating moderate problems, Level 4 indicating severe problems, and Level 5 indicating extreme problems).^{27,31}

The subject selects an answer for each of the 5 dimensions considering the response that best matches his or her health "today." The descriptive system can be represented as a health state. The EQ-VAS self-rating records the respondent's own assessment of his or her overall health status at the time of completion, on a scale of 0 to 100.

The time taken to complete the questionnaire varies with age, health status, and setting but is likely to be around 1 minute.

9.2.2. Endpoints

9.2.2.1. Primary Endpoint

The primary efficacy endpoint is the change in the MADRS total score as measured by the change from baseline (Day 1 prior to randomization) to the end of the 4-week double-blind induction phase.

9.2.2.2. Secondary Endpoints

- Proportion of responders ($\geq 50\%$ reduction from baseline in MADRS total score) at the end of the 4-week double-blind induction phase
- Proportion of subjects in remission (MADRS ≤ 12) at the end of the 4-week double-blind induction phase
- Change from baseline (Day 1 prior to randomization) to the end of the 4 week double-blind induction phase in:
 - Severity of depressive illness, using the CGI-S
 - Health-related quality of life and health status, as assessed by the EQ-5D-5L

9.3. Pharmacokinetics

Whole blood samples will be used to evaluate the PK of esketamine. Plasma collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

9.3.1. Evaluations

Venous blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of esketamine, noresketamine, and other metabolites (if warranted) at the time points specified in the Time and Events Schedule. The exact dates and times of PK blood sampling must be recorded.

9.3.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of esketamine (and noresketamine, if warranted) using a validated, specific, achiral, and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method by or under the supervision of the sponsor. If required, some plasma samples may be analyzed to document the presence of other analytes (eg, circulating metabolites or denatonium) using a qualified research method. In addition, plasma PK samples may be stored for future analysis of the metabolite profile.

The bioanalytical report, including a description of the assay and a summary of the assay performance data, will be included in the final clinical study report as an addendum.

9.3.3. Pharmacokinetic Parameters

The plasma concentration-time data of esketamine (and noresketamine, if warranted) will be analyzed using population PK modeling. Typical population values of basic PK parameters (eg, esketamine clearance distribution volume) will be estimated together with the inter-individual variability. Effects of subject demographics, laboratory parameter values, and other covariates on the PK of esketamine will be explored. The results of the population PK analyses may be reported separately.

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

The relationship between MADRS total score (and possibly selected AEs as additional PD parameters) and PK metrics of esketamine may be evaluated. If there is any visual trend in graphical analysis, suitable models will be applied to describe the exposure-effect relationships. The results of the exposure-response evaluations will be presented in a separate report.

9.5. Biomarker, Pharmacogenomic (DNA), and Expression (RNA) Evaluations

During the study, blood will be collected for the assessment of biomarkers at the time points indicated in the Time and Events schedule. The biomarker blood samples should be collected prior to dosing. It is preferred that subjects adhere to a low fat diet on the day of sample collection.

In blood, biomarkers (protein, metabolite, and ribonucleic acid [RNA]) related to (but not limited to) the immune system activity, HPA axis activation, neurotrophic factors, and metabolic factors will be investigated. Biomarkers may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased.

The biomarker data obtained from this study may also be included in an ongoing cross-study analysis to investigate the relationship between depression severity and phenotypes and biomarkers.

Blood samples for DNA analyses will be collected at the time points indicated in the Time and Events Schedule for the assessment of genetic and epigenetic variation in genes in pathways relevant to depression (eg, HPA axis, inflammation, growth factors, monoamine transporters, ion channels, and circadian rhythm).

Genotyping will be conducted only on the screening sample; pharmacogenomic and epigenetic evaluations may be performed on any/all collected samples.

DNA samples will be used for research related to esketamine, oral antidepressants, TRD, or MDD. They may also be used to develop tests/assays related to esketamine, oral antidepressants, TRD, or MDD. Pharmacogenomic research may consist of the analysis of 1 or more candidate genes or of the analysis of genetic markers throughout the genome (as appropriate) in relation to esketamine, oral antidepressants, TRD, or MDD clinical endpoints.

Further information regarding handling, shipment, and labeling of biological samples will be provided in a separate laboratory manual.

9.6. Safety Evaluations

Details regarding the Independent Data Monitoring Committee are provided in Section [11.9](#).

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule.

There may be instances when a subject has started a scheduled clinic visit which includes a planned intranasal treatment session, but due to predose vital sign measurements (eg, blood pressure value), a decision is made to postpone/delay the intranasal treatment session within the visit window permitted per protocol. In such cases, all time points (including predose, if applicable) of the following assessments must be repeated on the actual intranasal treatment session day: vital signs (ie, blood pressure, pulse, respiratory rate, and temperature), 12-lead ECG, C-SSRS (since last visit), MOAA/S, pulse oximetry, BPRS+, and CADSS.

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section [12](#), Adverse Event Reporting.

TEAEs of special interest will be examined separately (please refer to Sections 3.2.6 and 11.8).

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

The use of local laboratories is allowed in cases where initiation of treatment or safety follow-up is time-critical and the central laboratory results are not expected to be available before the need to begin dosing or if actions need to be taken for safety reasons.

The following tests will be performed by the central laboratory, unless noted otherwise:

- Hematology Panel
 - hemoglobin
 - hematocrit
 - red blood cell (RBC) count
 - white blood cell (WBC) count with differential
 - platelet count

- Serum Chemistry Panel
 - sodium
 - potassium
 - chloride
 - bicarbonate
 - blood urea nitrogen (BUN)
 - creatinine
 - glucose
 - aspartate aminotransferase (AST)
 - alanine aminotransferase (ALT)
 - gamma-glutamyltransferase (GGT)
 - alkaline phosphatase
 - creatine phosphokinase (CPK)
 - calcium
 - phosphate
 - albumin
 - total protein
 - total bilirubin

- Urinalysis

Dipstick	Sediment (if dipstick result is abnormal)
-specific gravity	-red blood cells
-pH	-white blood cells
-glucose	-epithelial cells
-protein	-crystals
-blood	-casts
-ketones	-bacteria
-bilirubin	
-urobilinogen	
-nitrite	
-leukocyte esterase	

If dipstick result is abnormal, flow cytometry or microscopy will be used to measure sediment. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.

The following tests will be done at time points specified in the Time and Events Schedule or as required based on subject status (noted below):

- Lipid panel: total cholesterol, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, and triglycerides
- Urine Drug Screen: barbiturates, methadone, opiates, cocaine, cannabinoids (cannabinoids are only exclusionary at Day 1 predose), PCP, and amphetamine/methamphetamine
- Alcohol breath test
- Thyroid-stimulating hormone (TSH)
- Free thyroxine, only if required for abnormal TSH (see inclusion criterion 7.2 in Section 4.1)
- Calculation of creatinine clearance
- Glycated hemoglobin (HbA1c) test (Screening only)

Single, 12-Lead ECG

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs.

All ECG tracings will be sent to a central ECG laboratory. The ECGs will be read at the scheduled time points and summarized by a central ECG laboratory. The central ECG laboratory will send the sponsor an electronic copy of the data for inclusion in the clinical database. In addition, the investigator or sub-investigator is required to review all ECGs at the study visit to assess for any potential safety concerns or evidence of exclusionary conditions.

The subject must be discontinued at any time point after baseline (Day 1, predose) if:

- QTcF change from baseline is ≥ 60 msec AND QTcF > 480 msec, or
- QTcF > 500 msec.

Vital Signs (temperature, pulse/heart rate, respiratory rate, blood pressure)

Blood pressure and pulse/heart rate measurements will be assessed in a supine position with a completely automated device or using manual techniques.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

For further details regarding blood pressure, please see Guidance for Blood Pressure Monitoring on Intranasal Dosing Days (Section 6.2.1).

Tympanic temperature is recommended.

An automated device will be used for measurement of respiratory rate.

Pulse Oximetry

Pulse oximetry will be used to measure arterial oxygen saturation.

On each dosing day, the device will be attached to the finger, toe, or ear before the first nasal spray and then, after the first spray it will be monitored and documented. Any arterial oxygen saturation $< 93\%$ should be confirmed by an additional measurement on another part of the body.

On intranasal treatment session days, pulse oximetry will be performed every 15 minutes from predose to $t=1.5$ hours postdose. If oxygen saturation levels are $< 93\%$ at any time during the 1.5 hour postdose interval, pulse oximetry will be performed every 5 minutes until the level returns to $\geq 93\%$ or until the subject is referred for appropriate medical care, if clinically indicated.

Physical Examination, Height, Body Weight and Neck Circumference

Physical examinations, body weight, and height will be performed or measured per the Time and Events Schedule.

In addition, body mass index (BMI) will be calculated and neck circumference measured as part of the information required for the STOP-Bang questionnaire.

Nasal Examinations

Nasal examinations (including the upper respiratory tract/throat) will be conducted by a qualified healthcare practitioner. The objective of the examination at screening is to rule out any subjects with anatomical or medical conditions that may impede drug delivery or absorption.

Subsequent examinations will consist of a visual inspection of the nostrils, nasal mucosa, and throat for nasal erythema, rhinorrhea, rhinitis, capillary/blood vessel disruption, and epistaxis, and will be graded as follows: absent, mild, moderate, or severe.

Nasal Symptom Questionnaire

Subjects will complete a nasal symptom questionnaire. The nasal symptom questionnaire was developed by the sponsor to assess nasal symptoms following intranasal administration of study drug. The questionnaire asks about nasal symptoms, which are rated by the subject as none, mild, moderate, or severe, based on how he or she feels at the time of the assessment.

C-SSRS

The C-SSRS will be performed to assess potential suicidal ideation and behavior.

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment.⁶⁹ It is a clinical interview providing a summary of both suicidal ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening.

Two versions of the C-SSRS will be used in this study, the Baseline/Screening version, and the Since Last Visit version. The Baseline/Screening version of the C-SSRS will be used in the screening/prospective observational phase. In this version, suicidal ideation will be assessed at 2 time points (“lifetime” and “in the past 6 months”) and suicidal behavior will be assessed at 2 time points (“lifetime” and “in the past year”). All subsequent C-SSRS assessments in this study will use the Since Last Visit version, which will assess suicidal ideation and behavior since the subject’s last visit.

CADSS

The CADSS is an instrument for the measurement of present-state dissociative symptoms,⁵ and will be administered to assess treatment-emergent dissociative symptoms.

The CADSS consists of 23 subjective items, divided into 3 components: Depersonalization (Items 3 to 7, 20, and 23), derealization (Items 1, 2, 8 to 13, 16 to 19, and 21) and amnesia (Items 14, 15, and 22). Participant’s responses are coded on a 5-point scale (0=not at all to 4=extremely). CADSS has excellent inter-rater reliability and internal consistency.

BPRS+

Four items of the BPRS will be administered to assess potential treatment-emergent psychotic symptoms.

The BPRS is an 18-item rating scale that is used to assess a range of psychotic and affective symptoms, rated from both observation of the subject and the subject's own report.⁶¹ It reportedly provides a rapid and efficient evaluation of treatment response in clinic drug studies and in clinical settings.⁷⁵

Only the 4-item positive symptom subscale BPRS+ (ie, suspiciousness, hallucinations, unusual thought content, and conceptual disorganization) will be used in this study. It is highly sensitive

to change, and excellent inter-rater reliability can be achieved with training and a standard interview procedure.

MOAA/S

The MOAA/S will be used to measure treatment-emergent sedation, with correlation to levels of sedation defined by the American Society of Anesthesiologists (ASA) continuum.⁶⁴

The MOAA/S scores range from 0=no response to painful stimulus (corresponds to ASA continuum for general anesthesia) to 5=readily responds to name spoken in normal tone (awake; corresponds to ASA continuum for minimal sedation).

On each intranasal treatment session day, the MOAA/S will be performed every 15 minutes from predose to t=+1.5 hours postdose.

- If the score is ≤ 3 at any time during the 1.5 hour postdose interval, the MOAA/S will be performed every 5 minutes until a score of 4 is reached (at which point a frequency of every 15 minutes can be resumed until t=+1.5 hours post dose).
- If a subject does not have a score of at least 5 at t=+1.5 hours postdose, they should continue to be monitored. For subjects with a score of 4, the assessment should be repeated every 15 minutes. And for subjects with a score of ≤ 3 , the assessment should be repeated every 5 minutes until the score returns to 5 or the subject is referred for appropriate medical care, if clinically indicated.

CGADR

The CGADR will be used to measure the subject's current clinical status and is the clinician's assessment of the readiness to be discharged from the study site.

The clinician will answer "Yes" or "No" to the question "*Is the subject considered ready to be discharged based on their overall clinical status (eg, sedation, blood pressure, and other adverse events)?*"

On intranasal treatment session days, the CGADR will be performed at 1 hour, and 1.5 hours postdose; if the response is not "Yes" at 1.5 hours postdose, the assessment will be repeated every 15 minutes until a "Yes" response is achieved or until the subject is referred for appropriate medical care if clinically indicated. **A subject should not be discharged prior to the 1.5 hour time point.**

On all intranasal treatment session days, subjects must remain at the clinical site until study procedures have been completed and the subject is ready for discharge.

PWC-20

The PWC-20 will be administered to assess potential withdrawal symptoms following cessation of intranasal esketamine treatment. An assessment will be performed for all subjects on Day 25 to establish a baseline prior to discontinuation of intranasal esketamine treatment (if applicable). In order to better assess potential withdrawal symptoms from the intranasal medication it is

recommended that the oral antidepressant medication be continued for the 2 weeks of the follow-up phase unless determined as not clinically appropriate.

The PWC-20 is a 20-item simple and accurate method to assess potential development of discontinuation symptoms after stopping of study drug. The PWC-20 is a reliable and sensitive instrument for the assessment of discontinuation symptoms.⁷² Discontinuation symptoms occur early and disappear rather swiftly, depending upon speed of taper, daily medication dose, and drug elimination half-life.

BPIC-SS

The BPIC-SS is a patient-reported outcome measure that was developed to identify an appropriate bladder pain syndrome/interstitial cystitis population for clinical studies evaluating new treatments for bladder pain syndrome.⁴⁰

The BPIC-SS will be used to monitor subjects for potential symptoms of cystitis, bladder pain, and interstitial cystitis.

The BPIC-SS includes 8 questions with a recall period of the past 7 days, and addresses key symptoms identified by subjects with BPS including symptom concepts of pain and/or pressure of the bladder, and urinary frequency. Subjects respond to items using a 5-point scale (0=never, 1=rarely, 2=sometimes, 3=most of the time, 4=always for frequency-based questions, and 0=not at all, 1=a little, 2=somewhat, 3=moderately, and 4=a great deal for items related to bother associated with symptoms). Question 8 records the worst bladder pain in the last 7 days using a 0-10 numerical rating scale. A total score is calculated by adding up the numbers beside the response options chosen by the subject. The range of scores for the scale is 0 to 38.

A total score of 19 or more has demonstrated good sensitivity/specificity and is considered a relevant cut-off to distinguish those with significant bladder symptoms and/or cystitis.⁴⁰

If any items are missing, a total score cannot be calculated.

In the current study, if a subject has a score >18 on the BPIC-SS scale and there is no evidence of urinary tract infection based on urinalysis and microscopy, he or she will be referred to a specialist for further evaluation. If a subject is determined to have a diagnosis of ulcerative cystitis, the subject must be discontinued from the study and followed up with appropriate medical care. As such, in addition to urinalysis, a urine culture should also be obtain if BPIC-SS score is >18 on applicable study day.

Cognition Testing: Computerized Cognitive Battery and HVLT-R

The computerized cognitive battery provides assessment of multiple cognitive domains, including attention, visual learning and memory, and executive function. The tests use culture-neutral stimuli, enabling use in multilingual/multicultural settings. The computerized battery includes:

- Simple and choice reaction time tests; scored for speed of response (mean of the log 10-transformed reaction times for correct responses)
- Visual episodic memory; visual recall test scored using arcsine transformation of the proportion of correct responses
- Working memory (n-back); scored for speed of correct response (mean of the log 10-transformed reaction times for correct responses)
- Executive function; maze/sequencing test, scored for total number of errors

All measures have been validated against traditional neuropsychological tests and are sensitive to the effects of various drugs on cognitive performance, including alcohol and benzodiazepines. Completing the cognitive battery requires approximately 25 minutes.

The HVLTR, a measure of verbal learning and memory, is a 12-item word list recall test. Administration includes 3 learning trials, a delayed recall (20-minute) trial, and a 24-word recognition list (including 12 target and 12 foil words).⁴ The test administrator reads instructions and word lists aloud, and records words recalled/recognized by the subject. Scores include learning, delayed recall, and recognition. The HVLTR is a well-validated and widely used measure of verbal episodic memory.⁴⁹

The tests will be administered in the following order: HVLTR, computerized cognitive test battery, and HVLTR Delayed.

All subjects will complete a practice session for the computerized cognitive battery during the screening/prospective observational phase. There is no practice session for the HVLTR.

UPSIT

To assess any potential treatment-emergent effects on the sense of smell, olfactory function will be qualitatively and quantitatively assessed using a validated standardized olfactory test prior to and at specified time points during the study.

The UPSIT assesses a subject's ability to identify odors. This standardized test, the most widely used olfactory test in the world, is derived from basic psychological test measurement theory and focuses on the comparative ability of subjects to identify odorants at the suprathreshold level. The UPSIT consists of 3 envelope-sized booklets, each containing 10 "scratch and sniff" odorants embedded in 10- to 50- μ m polymer microcapsules positioned on brown strips at the bottom of the pages of the booklets. The internal consistency and test-retest reliability coefficients of this instrument are >0.90 .^{22,21} Numerous studies have shown this and related tests to be sensitive to subtle changes in smell function associated with multiple etiologies, including those due to viruses, head trauma, and a number of neurodegenerative diseases.

The UPSIT test will be administered bilaterally (ie, both nostrils at the same time). Testing will occur during the screening/prospective observational phase to establish a subject's baseline sensitivity. The degree of change from this baseline will be determined subsequently over time. The percent change from baseline will serve as the dependent measure for each subject for each test.

9.7. Other Evaluations

MINI

Subjects will undergo MINI (a brief, structured diagnostic interview) to confirm the diagnosis of MDD and to determine if there are other psychiatric conditions present. It has an administration time of approximately 15 minutes.

MGH-ATRQ

The MGH-ATRQ is used to determine treatment resistance in MDD.¹⁸

The MGH-ATRQ evaluates the adequacy of duration and dosage of all antidepressant medications used for the current major depressive episode. In addition, the MGH-ATRQ assesses the degree of improvement on a scale from 0% (not improved at all) to 100% (completely improved). The MGH-ATRQ will be completed by the clinician, in collaboration with the subject.

MMSE

The MMSE is a validated, brief examination that rates subjects on orientation (total score, 10), registration (total score, 3), attention and calculation (total score, 5), recall (total score, 3), and language (total score, 9).³² The MMSE is effective as a screening tool for cognitive impairment with older community dwelling, hospitalized and institutionalized adults. The maximum score is 30. The MMSE will be completed at screening only. A total score <25 or <22 for those subjects with less than an equivalent of a high school education, will be used in the current study in order to exclude subjects with potential neurodegenerative disorder.

STOP-Bang Questionnaire

Snoring, Tiredness, Observed Apnea, High Blood Pressure, Body Mass Index, Age, Neck Size, Gender (STOP-Bang) Questionnaire

The STOP-Bang questionnaire is a concise, easy-to-use, validated, and sensitive screening tool for obstructive sleep apnea (OSA). This questionnaire has 8 items which address key risk factors for obstructive sleep apnea: snoring, tiredness, observed breathing interruption during sleep, high blood pressure, body mass index, age, neck size, and gender. The STOP-Bang questions do not specify a recall period. Subjects will answer yes or no to questions about snoring, tiredness, observed breathing interruption, and high blood pressure (these are the STOP items in the STOP-Bang acronym); this takes approximately 1 minute.⁶

Study site staff will answer yes or no to questions about body mass index (more than 35 kg/m²?), age (older than 50 years?), neck circumference (larger than 17 inches [43 cm] in men, or larger than 16 inches [41 cm] in women?), and gender (male?).

The total STOP-Bang score is calculated by summing the number of positive responses, yielding a score range of 0 to 8. A score of ≥ 5 on the STOP-Bang indicates a moderate to severe risk for OSA (AHI of >30).⁶

Site Independent Qualification Assessment

Independent psychiatrists/psychologists will perform the Site Independent Qualification Assessment in the screening/prospective observational phase for all subjects to confirm diagnosis of depression and eligibility for the study.⁸⁶

Further information regarding this assessment will be provided to sites in a separate document.

IDS-C₃₀

The 30-item IDS-C₃₀ is designed to assess the severity of depressive symptoms.⁷⁶ The IDS assesses all the criterion symptom domains designated by the DSM-5 to diagnose a major depressive episode. These assessments can be used to screen for depression, although they have been used predominantly as measures of symptom severity. The 7-day period prior to assessment is the usual time frame for assessing symptom severity. The psychometric properties of the IDS-C₃₀ have been established in various study samples.⁸⁶

PAQ

Subjects' adherence to their oral antidepressant treatment regimen during the screening/prospective observational phase will be assessed using the PAQ. It is a brief, 2-item self-report scale, developed at the University of Texas Southwestern Medical Center to assess how often the subject has taken, and whether he or she has made any changes to, his/her antidepressant treatment regimen in the last 2 weeks. The total score is based on the response selected to Question 1, and is interpreted as 0-1=adherent and 2 or more=nonadherent.⁵⁸

9.8. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (USP) (or equivalent) and charged with a volume equal to the dead space volume of the lock.

Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the double-blind induction phase of the study if he or she has completed the MADRS assessments at the end of the 4-week double-blind induction phase (ie, Day 28 MADRS).

Subjects who prematurely discontinue study treatment for any reason before completion of the double-blind induction phase will not be considered to have completed the double-blind induction phase of the study.

10.2. Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent (Note: See “Withdrawal of Consent” section below; this should only be selected as a reason for withdrawal if the subject does not agree to any further study assessments or procedures. If the subject is agreeable to participating in the Early Withdrawal visit and the follow-up phase, another reason for withdrawal should be selected.)
- Violation of protocol procedures (determined on a case-by-case basis)
- Blind is broken (double-blind induction phase)
- Lack of efficacy
- The investigator or sponsor believes (eg, that for safety or tolerability reasons such as an adverse event) it is in the best interest of the subject to discontinue the study. See also guidance on blood pressure monitoring on intranasal dosing days (Section 6.2.1).
- At any time point after baseline (Day 1, predose), the subject has a:
 - QTcF change from baseline ≥ 60 msec AND QTcF > 480 msec, or
 - QTcF > 500 msec
- Death
- Study is terminated by Sponsor for futility

If the subject withdraws from the study before the end of the double-blind induction phase, an Early Withdrawal visit is to be performed.

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. This should include at least 3 telephone calls, certified letters, email requests, etc. To ensure access to follow-up subjects, the study sites should attempt to obtain both primary and secondary telephone contact numbers (eg, home, work, and mobile phone numbers including phone numbers of relatives), as well as other contact information (eg, e-mail addresses) from subjects before randomization. In addition, the study site should emphasize the importance of follow-up

information to the subject before randomization. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Subjects who withdraw will not be replaced.

Withdrawal of Consent

Every effort will be made in the study to ensure withdrawal of consent is not selected as a reason for discontinuation when in fact the subject withdrew for an identifiable reason (eg, due to an adverse event or lack of efficacy).

Subjects who wish to withdraw from the study should be asked if they are agreeable to continue to an early withdrawal visit (if withdrawing from the double-blind induction phase) and the follow-up phase, or to be contacted to collect follow-up information. Subjects who are not agreeable to follow-up contact will be withdrawn from the study as “withdrawal of consent.” Subjects who no longer wish to take study drug but agree to provide follow-up information will be withdrawn from the double-blind induction phase with the reason noted as “Other” and will specify the reason why.

For a subject who withdraws consent, it is recommended that the subject withdraw consent in writing; if the subject refuses or is physically unavailable, the study site should document and sign the reason for the subject’s failure to withdraw consent in writing and maintain it with the subject’s source records.

The investigator will be responsible for making all required notifications to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

10.3. Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

11.1. Subject Information

The primary efficacy and safety analysis sets are defined below.

- **Full Analysis Set:** All randomized subjects who receive at least 1 dose of intranasal study medication and 1 dose of oral antidepressant medication in the double-blind induction phase.

- **Safety Analysis Set:** All randomized subjects who receive at least 1 dose of intranasal study medication or 1 dose of oral antidepressant medication in the double-blind induction phase.

11.2. Sample Size Determination

The maximum sample size planned for this study was calculated assuming a treatment difference after 4 weeks of treatment in the double-blind induction phase of 6.5 points in MADRS total score between esketamine and the active comparator, a standard deviation of 12, a 1-sided significance level of 0.025, and a drop-out rate of 25%. A maximum of about 74 subjects will need to be randomized to each treatment group to achieve 80% power using a fixed design with no interim analysis. The treatment difference and standard deviation used in this calculation were based on results of Panel A of the ESKETINTRD2003 study and clinical judgment.

As detailed below, an interim analysis is planned to re-estimate sample size or to stop the study due to futility.

11.3. Interim Analysis for Sample Size Re-estimation or Stopping for Futility

One unblinded interim analysis will be performed 4 weeks after randomizing 50 subjects in the study (approximately 25 per treatment group). It is projected that at that time approximately 36 subjects in the full analysis set would have completed the double-blind induction phase of the study (approximately 18 subjects per treatment group). The dropout rate will be monitored to ensure that a sufficient number of subjects are included in the interim analysis. As the assumptions of the expected treatment difference and variability may or may not be upheld, the purpose of the interim analysis is to either re-estimate sample size or to stop the study due to futility. The sample size may be adjusted to achieve the desired power while maintaining control of the overall Type I error. The maximum sample size planned for this study is 74 per treatment group.

A rigorous interim statistical analysis plan (SAP) and charter will be developed detailing the algorithm for a sample size re-estimation based on the interim data and how the analysis will be executed. An IDMC will perform the interim analysis and will make recommendations for any sample size adjustment based on the rules defined in the interim SAP. Any changes to sample size will be communicated by the IDMC (or the statistician from the Statistical Support Group) to the IWRS vendor to ensure that the appropriate number of subjects is enrolled in the study. None of the esketamine team members or staff members at the investigational sites conducting the clinical study will be informed of the results of the interim analysis or of any specific sample size adjustment resulting from this interim analysis. However, the Clinical Supplies group will be informed of the decision made at the interim analysis so that only the required amount of study medication will be packaged.

Procedures will be in place to ensure that the results of the interim analysis do not influence the conduct of the study, investigators, or subjects.

11.4. Efficacy Analyses

Efficacy analyses will be performed on the FAS, which will include all randomized subjects who receive at least 1 dose of intranasal study medication and 1 dose of oral antidepressant medication during the double-blind induction phase.

With the exception of the European Union (EU) dossier, the primary efficacy variable, change from baseline in MADRS total score at Week 4 in the double-blind induction phase, will be analyzed using MMRM. The model will include baseline MADRS total score as a covariate, and treatment, country, class of antidepressant (SNRI or SSRI), day, and day-by-treatment interaction as fixed effects, and a random subject effect. Comparison of the intranasal esketamine plus oral antidepressant arm versus oral antidepressant plus intranasal placebo will be performed using the appropriate contrast.

For the EU dossier, the primary efficacy analysis will be based on an analysis of covariance (ANCOVA) model using last observation carried forward (LOCF) data. The model will include factors for treatment, country, and class of oral antidepressant (SNRI or SSRI) and baseline MADRS total score as a covariate. Comparison of the intranasal esketamine plus oral antidepressant arm versus intranasal placebo plus oral antidepressant will be performed using the appropriate contrast.

Response and remission rates will be summarized at each visit.

The ranks of change from baseline in CGI-S scores at the end of the double-blind induction phase will be analyzed based on LOCF data using an ANCOVA model, with country and class of antidepressant (SNRI or SSRI) as factors, and the baseline score (unranked score) as the covariate.

Dimension scores of EQ-5D-5L, health status index, and the overall health status score will be summarized over time.

Additionally, scores of all efficacy endpoints will be summarized for all visits in the double-blind induction phase. Summaries will be provided to show consistency of effect among relevant subgroups (eg, antidepressant class SNRI and SSRI).

11.5. Pharmacokinetic Analyses

Plasma esketamine (and noresketamine, if warranted) concentrations will be listed for all subjects. The plasma concentration-time data of esketamine (and noresketamine, if warranted) will be analyzed using population PK modeling. Data may be combined with those of other selected studies to support a relevant structural model. Typical population values of basic PK parameters will be estimated together with the inter-individual variability. Effects of subject demographics, laboratory parameter values, and other covariates on the PK of esketamine will be explored. The results of the population PK analyses may be reported separately.

11.6. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between MADRS total score (and possibly selected adverse events as additional PD parameters), and PK metrics of esketamine may be evaluated. If there is any visual trend in graphical analysis, suitable models will be applied to describe the exposure-effect relationships. The results of the PK/PD analyses may be reported separately.

11.7. Biomarker and Pharmacogenomic Analyses

Baseline biomarker values and changes from baseline biomarker values to the time points specified in the Time and Events Schedule will be summarized. Exploratory analyses may include comparison of biomarker measures between the treatment groups and correlation with baseline and change from baseline biomarker values in the efficacy and other measures. Additional exploratory analyses may also include relationship of baseline and change from baseline in biomarker measures to clinical response, maintenance/stabilization of response, relapse, and nonresponse.

Pharmacogenomic analyses may include candidate gene analyses or genome-wide association analyses in relation to treatment response, maintenance/stabilization of response, relapse, and nonresponse, and MDD/TRD. Expression analyses may include testing of known messenger RNA/microRNA (mRNA/miRNA) transcripts or transcriptome-wide analysis in relationship to antidepressant treatment response and MDD/TRD.

Details of the analysis plan and summary of results from both biomarker and pharmacogenomics analyses will be reported separately.

11.8. Safety Analyses

Safety data will be analyzed for the double-blind induction phase using the safety analysis set. The safety data from the follow-up phase will be summarized separately.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the MedDRA. All reported adverse events with onset during the double-blind induction phase (ie, TEAEs, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. Adverse events occurring during the follow-up phase will be summarized separately.

TEAEs of special interest will be examined separately (please refer to Section 3.2.6). Adverse events of special interest will be further listed in the SAP.

Subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event will be summarized separately.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point in each phase of the study. Changes from baseline results will be presented. Frequency tabulations of the abnormalities will be provided. Listings of subjects with laboratory results outside the reference ranges and markedly abnormal results will also be provided.

ECG

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and change from baseline values.

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline, and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods QT corrected according to Fridericia's formula (QTcF), which will be the primary correction factor, and QT corrected according to Bazett's formula (QTcB).^{39,76}

Descriptive statistics of QTc intervals and changes from double-blind baseline will be summarized at each scheduled time point. The percentage of subjects with QTc interval >450 msec, >480 msec, or >500 msec will be summarized, as will the percentage of subjects with QTc interval increases from baseline <30 msec, 30-60 msec, or >60 msec.

All important abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves).

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, pulse oximetry, and blood pressure (systolic and diastolic) (supine) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

Nasal Examination

Changes in findings from the baseline nasal examination (including the upper respiratory tract/throat) will be listed by treatment group. Examinations will provide ratings (absent, mild, moderate, or severe) that are based on a visual inspection of the nostrils, nasal mucosa, and throat for nasal erythema, rhinorrhea, rhinitis, capillary/blood vessel disruption and epistaxis. A shift table for changes from double-blind baseline in ratings for each examination will be presented by treatment group.

Nasal Symptom Questionnaire

Scoring from the nasal symptom questionnaire will be summarized descriptively for each scheduled time point by treatment group.

C-SSRS

Suicide-related thoughts and behaviors based on the C-SSRS will be summarized by treatment group in incidence and shift tables. Separate endpoints for suicidal ideation and suicidal behavior will be defined and summarized descriptively by treatment group. Missing scores will not be imputed.

CADSS, BPRS+, and MOAA/S

Descriptive statistics of each of the scores and changes from predose will be summarized at each scheduled time point.

CGADR, PWC-20, UPSIT, BPIC-SS

Descriptive statistics of each of the scores and changes and/or percent changes from baseline will be summarized at each scheduled time point.

Cognition Testing

Descriptive statistics of each of the cognitive domain scores and changes from baseline will be summarized at each scheduled time point.

11.9. Independent Data Monitoring Committee

An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. In addition, the committee will review 1 interim analysis for a sample size re-estimation. The committee will meet every 6 months to review safety data and will meet once to review efficacy data after the interim analysis has been completed. After the reviews, the IDMC will make recommendations regarding the continuation of the study or, in the case of the interim analysis for efficacy, to either stop the study due to futility or to adjust the sample size to achieve the desired power while maintaining control of the overall Type I error. The details will be provided in a separate IDMC charter.

The IDMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The IDMC responsibilities, authorities, and procedures will be documented in its charter.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (for example, the subject was at risk of death at the time of the event. “Life threatening” does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For esketamine, the expectedness of an adverse event will be determined by whether or not it is listed in the Reference Safety Information Section of the Investigator's Brochure.

For duloxetine, escitalopram, sertraline, and venlafaxine XR, the expectedness of an adverse event will be determined by whether or not it is listed in the SmPC or US prescribing information.^{24,23,28,29,81,82,87,88}

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions**Not Related**

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety), with the exception of pregnancy which will be reported up to 6 weeks after the last dose of study medication (females) or 90 days after the last dose of study medication (partners of male participants). Serious adverse events, including those spontaneously reported to the investigator, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in [Attachment 4](#).

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event

management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)
- Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:
 - Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility).
 - Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the subject during a treatment period.

The cause of death of a subject in a study, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

12.3.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators,

and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 1 business day after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

Intranasal Study Drug

Esketamine will be supplied as a clear, colorless intranasal solution of esketamine HCl (16.14% weight/volume [w/v]; equivalent to 14% w/v of esketamine base) in a nasal spray pump. The solution will consist of 161.4 mg/mL esketamine HCl (equivalent to 140 mg of esketamine base) formulated in 0.12 mg/mL ethylenediaminetetraacetic acid (EDTA) and 1.5 mg/mL citric acid at a pH of 4.5 in water for injection. It is provided in a nasal spray pump, which delivers 16.14 mg esketamine HCl (14 mg esketamine base) per 100- μ L spray. Each individual nasal spray pump (device) contains a total of 28 mg (ie, 2 sprays).

The placebo solution will be supplied as a clear, colorless intranasal solution of water for injection, with a bittering agent (denatonium benzoate [Bitrex[®]] at a final concentration of 0.001mg/mL) added to simulate the taste of the intranasal solution with active drug. The placebo solution will be provided in matching nasal spray pump devices. Benzalkonium chloride is added as a preservative at a concentration of 0.3 mg/mL. Each individual nasal spray pump (device) contains 2 sprays.

Esketamine and placebo will be manufactured and provided under the responsibility of the sponsor. Please refer to the Investigator's Brochure for a list of excipients.⁴²

Oral Antidepressant Medications

Duloxetine

Duloxetine 30 mg will be obtained from commercial stock and provided under the responsibility of the sponsor. Refer to the SmPC/USPI for the physical description and a list of excipients.^{24,23}

Escitalopram

Escitalopram 10mg will be obtained from commercial stock and provided under the responsibility of the sponsor. Refer to the SmPC/USPI for the physical description and a list of excipients.^{28,29}

Sertraline

Sertraline 25 mg and 50 mg (as applicable) will be obtained from commercial stock and provided under the responsibility of the sponsor. Refer to the SmPC/USPI for the physical description and a list of excipients.^{81,82}

Venlafaxine XR

Venlafaxine 37.5mg and 75 mg (as applicable) will be obtained from commercial stock and provided under the responsibility of the sponsor. Refer to the SmPC/USPI for the physical description and a list of excipients.^{87,88}

14.2. Packaging

Intranasal Study Drug

Study drug (ie, intranasal esketamine and placebo solution) will be supplied by the sponsor in a bi-dose nasal spray device. The devices will contain 230 μ L (of which \sim 30 μ L is the residual volume). Each device delivers 16.14 mg esketamine HCl (14 mg esketamine base) or 0.1 μ g of denatonium benzoate per 100 μ L spray.

Each nasal spray device will be individually packaged in a blister tray and subsequently put into a carton box. Each carton box constitutes a non-child-resistant subject kit, labeled with a unique medication kit number.

Device for Practicing Intranasal Study Drug Administration

The demonstration intranasal device will also be supplied by the sponsor and will contain placebo solution. Subjects will practice spraying (into the air, not intranasally).

Oral Antidepressant Medication

Oral antidepressant tablets or capsules will remain in their commercial packaging.

If blisters are supplied; each blister will be packaged into a child-resistant dose pack to constitute a subject kit. All kits will be labeled with a unique medication kit number, and labeled according to applicable regulatory requirements.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

Study drug will be stored at the study site in a secure area with restricted access until dispensed to the subjects.

All study drug must be stored at controlled temperatures as indicated on the product-specific labeling.

Refer to the pharmacy manual/study site investigational product manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study.

The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug.

The study drug administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the investigational product destruction form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the investigational product destruction form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject.

Whenever a subject brings his or her study drug to the study site for pill count (ie, compliance check), this is not seen as a return of supplies.

Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Practice intranasal devices
- Investigator's Brochure for esketamine
- Local prescribing information for oral antidepressant options in double-blind induction phase
- Investigational Product (IP) Binder, including the IP Procedures Manual
- Laboratory manual and materials
- Clinician-administered and patient-reported outcome assessments
 - Paper versions, as applicable
 - Electronic devices and associated materials
- IWRS Manual
- ECG equipment and associated materials (eg, manual)
- Instructions for Use documents (subject and healthcare provider versions) for intranasal study medication
- Rater qualifications/requirements for select clinician-administered assessments
- Computerized cognitive battery and HVLTR, and all associated equipment and materials
- Device to measure respiratory rate
- Procedural documents for Site Independent Qualification Assessment
- Procedural documents for independent, remote rater interviews
- Guidance on recommended order of study procedures
- MGH-ATRQ guidance document
- SmPCs of the active comparators: Duloxetine, escitalopram, sertraline, and venlafaxine XR
- Subject diary

16. ETHICAL ASPECTS

16.1. Study-specific Design Considerations

Clinical Study in Treatment-resistant Major Depression

Major depressive disorder is a common, severe, chronic, and often life-threatening illness. It is now the leading cause of disability worldwide. There is a clear need to develop novel and improved therapeutics for treatment-resistant depression in the elderly population.

Studies with esketamine have shown robust antidepressant effects in several clinical studies and it has been well tolerated in these clinical studies.

Selection of Subjects

The primary aim of the study is to evaluate the efficacy of intranasal esketamine plus an oral antidepressant for the treatment of TRD in the elderly population. Thus, the study cannot be completed in healthy subjects.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation.

For eligibility, subjects must have had nonresponse to at least one prior antidepressant treatment and be currently taking an antidepressant treatment at the start of the screening/prospective observational phase that will be continued as prospective treatment in the screening/prospective/observational phase. Only subjects with nonresponse to their current antidepressant treatment after 4 weeks of prospectively observed treatment (for a total duration of antidepressant treatment of at least 6 weeks by the end of the screening/prospective observational phase), will be eligible to proceed to the double-blind induction phase, when all subjects will receive a new oral antidepressant in addition to intranasal esketamine or placebo. Subjects will receive 4 weeks of treatment in the double-blind induction phase and at the end of this phase, may participate in the open-label safety study (ESKETINTRD3004). Subjects who do not complete the double-blind induction phase of this study will not be eligible to participate in the ESKETINTRD3004 study. Subjects who choose not to enter the ESKETINTRD3004 study will proceed to the 2-week follow-up phase, during which all subjects will be provided with an additional 2-week supply of oral antidepressant and appropriate follow-up care will be arranged.

They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

Justification for Using Placebo

Intranasal placebo is being used as a double-blind for intranasal esketamine to maintain study blinding. All subjects will also receive a newly initiated oral antidepressant during the induction phase. Subjects will not be on placebo alone. Assessment of the potential efficacy of a new compound for the treatment of treatment-resistant major depression requires adequate and well-controlled clinical studies. This superiority study will compare intranasal esketamine plus a newly-initiated oral antidepressant to switching to an oral antidepressant as an active comparator.

Recent analyses have shown response to placebo varies considerably, from 10% to 55%. Therefore, there is a concern that randomized, controlled studies that rely on comparison with standard antidepressant treatments alone will generate unreliable results with limited assay sensitivity. However, some have considered it unethical to do placebo-controlled studies in major depression due to the potential risk of irreversible harm.⁷⁴ In a meta-analysis of drug studies

conducted in MDD, it was reported that adult subjects did not have higher rates of suicide behaviors or attempts in the placebo group compared with those receiving an active antidepressant.⁴⁷ These studies showed annual suicide rates of 0.8% on the investigational drug, 0.7% on the active comparator, and 0.4% on placebo. Thus, the risk of irreversible harm was not higher in the placebo arm compared with the active control arms.

Some subjects may decide not to participate in a placebo-controlled study due to the potential for increased distress and dysfunction from prolonged depression.

Therefore, the use of an active-controlled study allows for assessment of efficacy of a new compound to allow for scientifically meaningful results.

Moreover, the duration of the double-blind induction phase is relatively short (4-week duration). Subjects will visit the study site at least twice a week during the double-blind induction phase, and their symptoms will be carefully monitored during each study visit. Safety evaluations will include evaluation of suicidal ideation/behavior at each clinic visit. At any point in the study, the subject may withdraw consent or be removed from the study by the investigator if there are any clinical concerns.

Intranasal esketamine may not be available for subjects after the study. However, following completion of the double-blind induction phase, those subjects not continuing into the ESKETINTRD3004 study can be treated according to standard of care.

Precautions to Ensure Subject Safety in the Study

Subjects may participate in the study only if they have adequate capacity to give consent and after fully understanding the potential risks and giving an informed consent. Determination of capacity will be made by the study investigator. Subjects may discontinue the study at any time. The probability of receiving placebo and the concept of random assignment will be explained to the subject. The duration of the study is short, minimizing the time on intranasal placebo (which is being administered with a newly-initiated oral antidepressant). Potential disadvantages and adverse events of participating in the study and alternative treatment options will be discussed. For subjects who do not meet predefined response criteria during the study, clinical care will be arranged between the study investigator and their physician.

Compensation for any procedure will be fair per local standards and approved by the participating sites IRB in order to not offer any undue incentive to participate in the study.

Subjects will be carefully monitored during the study and subjects who are unable to tolerate study drug during the double-blind induction phase will be discontinued from the study. If the investigator judges it to be necessary to immediately stop study drug, he or she has the option to do so. Specific guidance is provided regarding blood pressure monitoring on intranasal dosing days (Section 6.2.1). In addition to a 12 lead ECG performed at Screening and pre-dose and post-dose on Day 1 (baseline), on subsequent dosing days all subjects will have an ECG at 1 hour post-dose.

Only subjects who had nonresponse to their current oral antidepressant treatment, where a clinician would consider changing it in the future due to lack of response, will be enrolled.

Only qualified and trained investigators will participate in the study.

The total blood volume to be collected is considered to be within the normal range allowed for this subject population over this time frame. The approximate total blood volume to be collected is approximately 117 mL, which will be less than a Red Cross blood donation.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board (IEC/IRB)

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Sponsor-approved training and informational materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no

consequences for subjects, data or study conduct), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-

related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, and agrees to allow his or her study physician to re-contact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory PK, PD, biomarker, DNA, and RNA research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand esketamine, oral antidepressants, to understand depression, to understand differential drug responders, and to develop tests/assays related to esketamine, oral antidepressants, and depression. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Use of Samples in Future Research]).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency

situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all sub-investigators
- Documentation of sub-investigator qualifications (eg, curriculum vitae)

- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Some subject- and clinician-completed scales and assessments designated by the sponsor will be recorded directly into an electronic device and will be considered source data.

The minimum source documentation requirements for Section 4.1, Inclusion Criteria, and Section 4.2 (Exclusion Criteria) that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

- Antidepressant treatment in the current episode of depression

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into eCRFs in English. Study site personnel must complete the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

The investigator must verify that all data entries in the eCRFs are accurate and correct. All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the eCRF (if applicable) and complete the query.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and uploading data transfers from external service providers into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or

designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with source documents (eg, hospital/clinic/physician's office medical records); a sample will be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related

documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, the monitor may contact the site by telephone for an update on study progress. It is expected that study-site personnel will be available to provide an update on the progress of the study at the site.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last study assessment for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development
- Study is terminated by the sponsor due to futility.

17.10. On-site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a

regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding esketamine or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of esketamine, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain eCRF data from all study sites that participated in the study and will represent uploaded data transferred from external service providers into the sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for

publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: Prohibited Concomitant Medications with Intranasal Study Medication (Esketamine or Placebo)

This list of medications is **not all-inclusive**; if necessary, please contact the medical monitor for any questions regarding a medication(s).

Please refer to the local prescribing information of the subject's oral antidepressant treatment for information regarding prohibited concomitant medications.

Except where specifically noted, the prohibited medications listed in the following table are prohibited from 1 week (or 5 half-lives, whichever is longer) prior to the first dose of intranasal study medication until after the last dose of intranasal study medication. Note: If a medication is part of the antidepressant treatment regimen being taken at the time of signing the ICF (ie, start of screening/prospective observational phase), dose adjustment is permitted per clinical judgment, but the oral antidepressant treatment is to remain at or above the minimum therapeutic dose (per the MGH-ATRQ) through the end of Week 4. . If the investigator determines it is clinically appropriate, the antidepressant medication may be tapered during the optional, up to 3-week, taper period.

Note in the following table: N, Prohibited; Y, Permitted, with restrictions (please refer to the column labeled "Comments" for additional guidance)

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
ADHD medications (eg, atomoxetine, guanfacine)	N	Y	Can be continued but must not be taken within 12 hours prior to the intranasal treatment session or for 2 hours after the intranasal treatment session.	Safety
Amantadine	N	N		PD interaction
Anorexiant (eg, phentermine, phendimetrazine)	N	N		Safety
Anticholinesterase inhibitors	N	N		Subject population is excluded
Anticonvulsants	N	N	Subjects with seizures are excluded. Use as adjunctive treatment for major depressive disorder (MDD) is prohibited. - Note: Anticonvulsants used for indications other than seizures may be allowed (eg, valproate for migraine, pregabalin)	Safety and PD interaction

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
Antidepressants (<i>other than the specific antidepressant started in the induction phase of the study</i>)	N	N	<ul style="list-style-type: none"> - Only 1 of the 4 predefined oral antidepressant treatment options are permitted - If a subject is taking a monoamine oxidase inhibitor (MAOI) during the screening/prospective observational phase, there must be a minimum washout interval of 2 weeks prior to the first dose of intranasal study medication. - Even if used for indications other than MDD (eg, trazodone or low dose tricyclic antidepressants for sleep), the use of any medication listed on the ATRQ, is not permitted during the treatment phase. 	Safety and PD interaction
Antipsychotics	N	N		PD interaction
Benzodiazepines (at dosages less than or equal to the equivalent of 6 mg/day of lorazepam) and non-benzodiazepine sleeping medication (including: zolpidem, zaleplon, eszopiclone, and ramelteon)	Y	Y	Prohibited within 12 hours prior to the start of each intranasal treatment session or cognition testing	Safety and PD interaction
Benzotropine	Y	N	Prohibited if use is continuous and prohibited within 12 hours prior to the start of cognition testing	Safety and PD interaction.
Chloral hydrate, melatonin, valerian	N	N		Safety and PD interaction
Clonidine	N	N		Safety and PD interaction
Corticosteroids (systemic)	Y	N	Inhaled, intranasal, topical, and ophthalmic steroids are not prohibited. Intermittent IM/IV corticosteroids are permitted (chronic use prohibited)	PD interaction
Cough/cold preparations/nasal solutions containing vasoconstrictors, decongestants	Y	Y	<p>Intranasally-administered decongestants (vasoconstrictors) should not be used from 1 hour prior to each intranasal study medication administration.</p> <p>Pseudoephedrine-containing oral products should not be used within 12 hours prior to an intranasal treatment session</p>	Safety and PD interaction

Drug Class	Episodic Use (as needed)	Continuous Use	Comments	Reason for Prohibition
CYP3A4 inducers - Potent	N	N	Subjects may not take a known potent inducer of hepatic CYP3A activity within 2 weeks of the first administration of intranasal study medication until at least 24 hours after the last intranasal dose of study medication. Examples (not all-inclusive): Efavirenz, nevirapine, barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort	PK
Dextromethorphan	N	N		PD interaction
Diphenhydramine	Y	N	Prohibited within 12 hours prior to the start of each intranasal treatment session	Safety
Ketanserin	N	N		Safety
Lithium	N	N		PD interaction
Memantine	N	N		PD interaction
Methyl dopa	N	N		Safety and PD Interaction
Metyrosine	N	N		Safety and PD interaction
Non-vitamin K antagonist oral anticoagulation agents (eg, dabigatran, rivaroxaban, apixaban)	N	N		Safety
Opioids	N	N		PD interaction
Psychostimulants (eg, amphetamines, methylphenidate, modafinil, armodafinil)	N	Y	Prescribed psychostimulants taken for indications other than MDD can be continued but must not be taken within 12 hours prior to the intranasal treatment session or for 2 hours after the intranasal treatment session.	Cardiovascular safety
Reserpine	N	N		PD interaction
Scopolamine	N	N		PD interaction
St. John's Wort	N	N		PD interaction and PK
Thyroid hormone supplement for treatment of thyroid condition only (not for depression)	N	Y		Safety
Thyroxine/triiodothyronine (T3), thyroid hormone prescribed for depression	N	N		PD interaction
Warfarin	N	N		Primary condition where used is excluded

Abbreviations: ADHD, attention deficit hyperactivity disorder; N, Prohibited; PD, pharmacodynamics; PK, pharmacokinetics; QTc, QT corrected; Y, Permitted, with restrictions (please refer to the column labeled "Comments" for additional guidance).

Attachment 2: New York Heart Association Classification of Cardiac Disease**New York Heart Association Classification of Cardiac Disease**

Category	Description
Functional Capacity	
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Objective Assessment

- A No objective evidence of cardiovascular disease.
- B Objective evidence of minimal cardiovascular disease.
- C Objective evidence of moderately severe cardiovascular disease.
- D Objective evidence of severe cardiovascular disease.

Source: Criteria Committee of the New York Heart Association. Functional capacity and objective assessment. In: Dolgin M, ed. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 9th ed. Boston, MA: Little, Brown & Co; 1994, 253-255.

Attachment 3: Oral Antidepressant Titration Schedule for Double-Blind Induction Phase

The titration schedule for the 4 oral antidepressants to be used in the current study is provided below.

Prescribing Information: Oral Antidepressant (Active Comparator)	Titration Schedule			
	Week 1 (Starting Day 1)	Week 2 (Starting Day 8)	Week 3 (Starting Day 15)	Week 4 (Starting Day 22)
Duloxetine	30 mg	60 mg	60 mg	60 mg
Escitalopram	10 mg	10 mg	10 mg	10 mg
Sertraline	25 mg	50 mg	100 mg	150 mg
Venlafaxine XR	37.5 mg	75 mg	150 mg	150 mg

Attachment 4: Anticipated Events

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen. For the purposes of this study the following events will be considered anticipated events.^{24,23,28,29,42,81,82,87,88}

For esketamine and major depressive disorder (MDD) (including treatment-resistant depression [TRD]; based on DSM-5):

- Suicidal thinking, ideation, and behavior
- Sleep changes, difficulty sleeping, reduced sleep, abnormal sleep, tiredness, fatigue, and reduced energy
- Difficulty in sexual desire, performance or satisfaction
- Reduced appetite and weight changes (loss or increase)
- Activation or hypomania/ mania
- Excessive happiness
- Irritability, anger, and impulsive behavior
- Agitation, feeling anxious/anxiety, tension, panic attacks, and phobia

For esketamine, regarding events related to concomitant therapy with oral antidepressants (from the product's reference safety information/US prescribing information):

- Duloxetine
 - Most commonly observed adverse reactions from pooled studies of all indications (incidence of at least 5% and at least twice the incidence in placebo subjects) were nausea, dry mouth, somnolence, fatigue, constipation, decreased appetite, and hyperhidrosis (sweating). Duloxetine treatment worsens glycemic control in some subjects with diabetes.
 - Increased the risk compared to placebo of suicidal thinking and behavior; serotonin syndrome; hepatotoxicity; hepatic failure; orthostatic hypotension, syncope; abnormal bleeding; severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome (SJS); activation of mania or hypomania; hyponatremia.
- Venlafaxine XR
 - According to the US prescribing information, adverse events in short-term studies occurring in at least 5% of subjects receiving venlafaxine XR and at a rate twice the incidence in placebo subjects: abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, and anorexia), central nervous system complaints (dizziness, somnolence, and abnormal dreams), and sweating. Sustained hypertension is noted within Warnings and Precautions section.
 - Increased the risk compared to placebo of suicidal thinking and behavior, treatment-emergent insomnia and nervousness, activation of mania/hypomania, hyponatremia, mydriasis, abnormal bleeding, sustained hypertension, and serotonin syndrome.
- Escitalopram
 - Most commonly observed adverse reactions (incidence of approximately 5% or greater and approximately twice the incidence in placebo subjects) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence.
 - Increased the risk compared to placebo of suicidal thinking and behavior, serotonin syndrome, activation of mania/hypomania, hyponatremia and abnormal bleeding
- Sertraline

- Most common treatment-emergent AEs associated with sertraline (incidence of at least 5% for sertraline or at least twice the incidence in placebo subjects) were ejaculation failure, dry mouth, increased sweating, somnolence, tremor, dizziness, fatigue, pain, malaise, abdominal pain, anorexia, constipation, diarrhea/loose stools, dyspepsia, nausea, agitation, insomnia, and decreased libido, and serotonin syndrome.
- Increased the risk compared to placebo of suicidal thinking and behavior, activation/mania; bleeding events related to SSRI use (have ranged from ecchymosis, hematomas, epistaxis, and petechiae to life-threatening hemorrhages), hyponatremia (appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion [SIADH]); serotonin syndrome

Reporting of Anticipated Events

These events will be captured on the CRF and in the database, and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any event that meets serious adverse event criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

INVESTIGATOR AGREEMENT

JNJ-54135419 (esketamine)

Clinical Protocol ESKETINTRD3005 Amendment 3

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Jaskaran Singh, MD

Institution: Janssen Research & Development

Signature: _____ Date: 18 July 2016
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.